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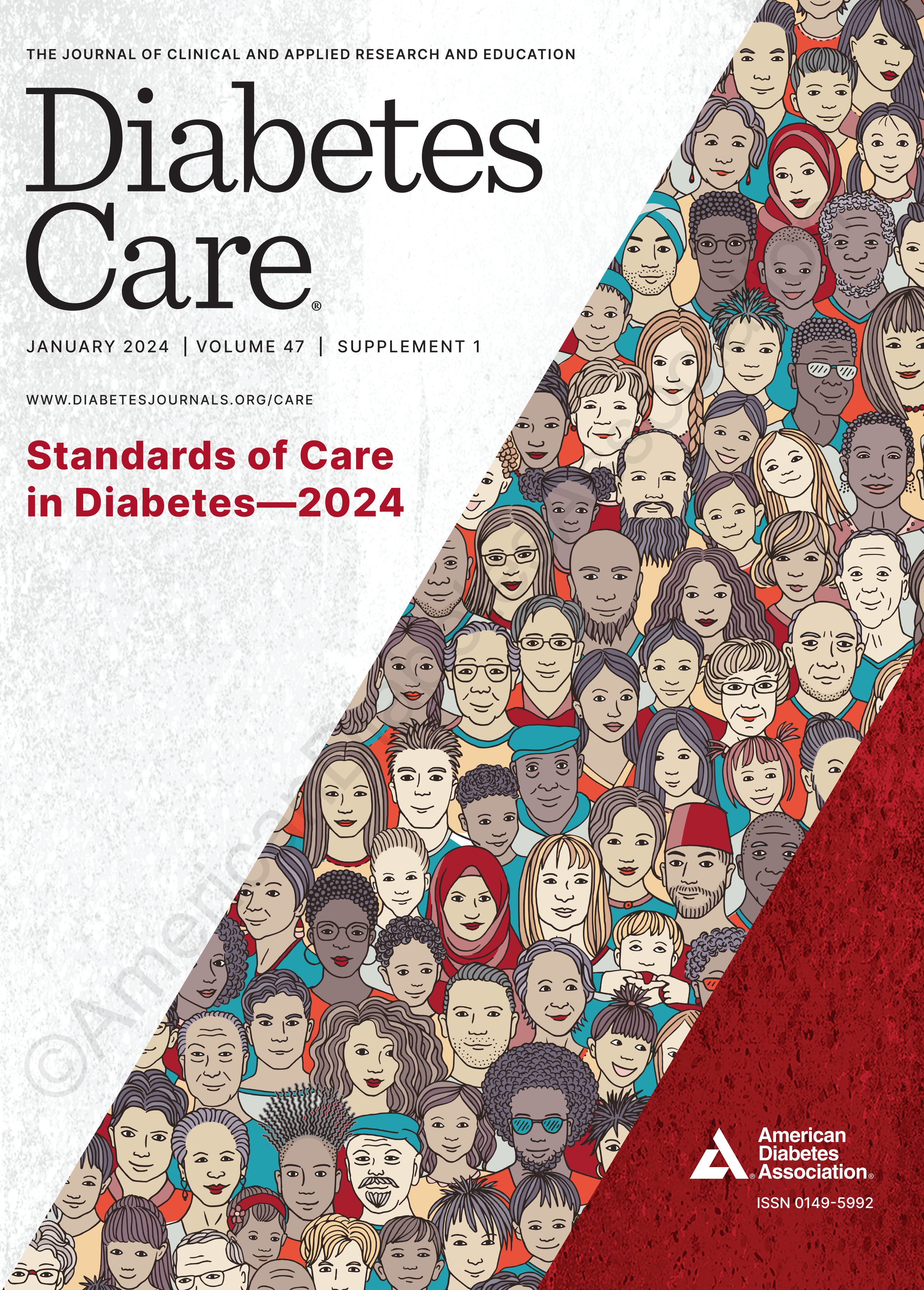
Standards of Care in Diabetes—2024



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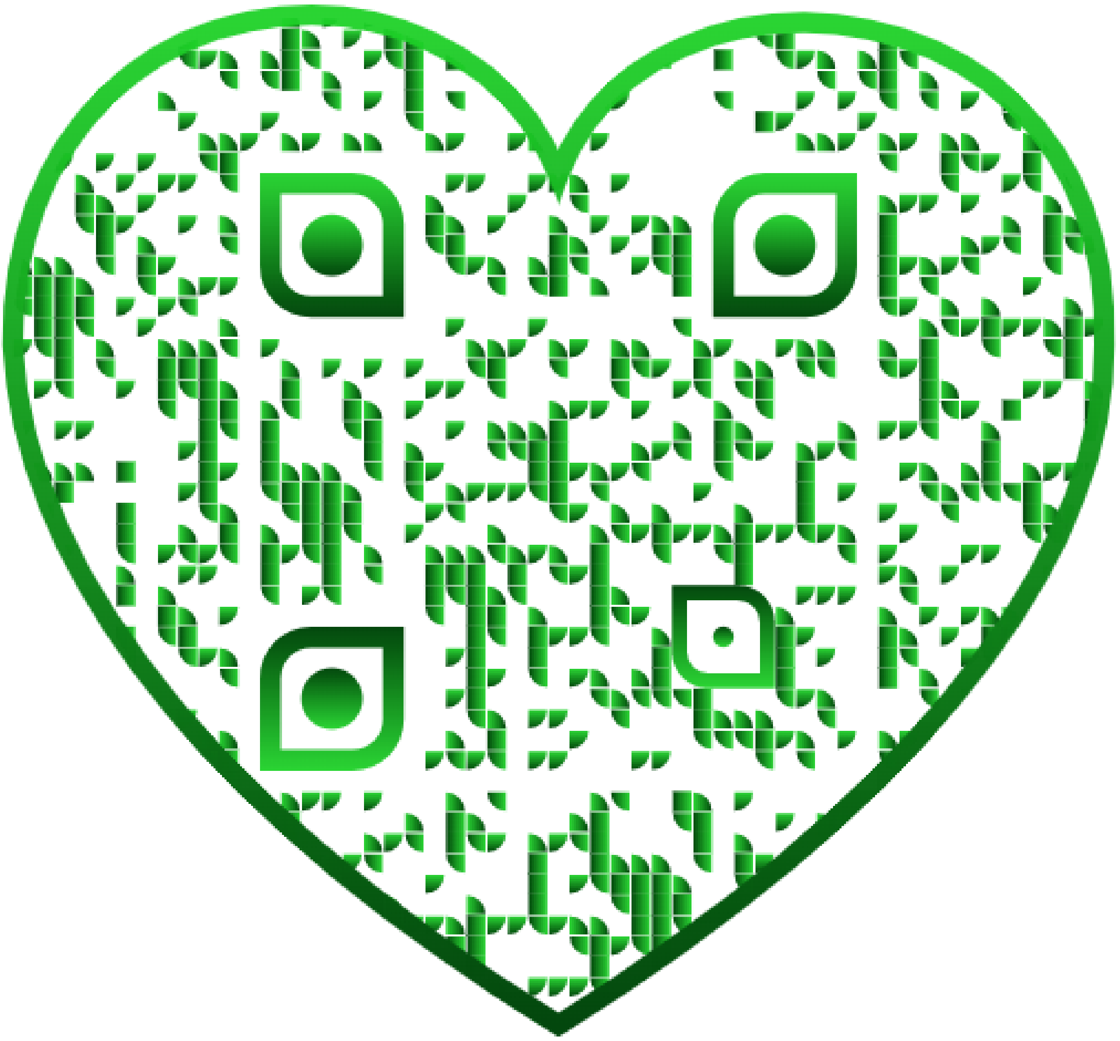

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Standards of Care in Diabetes—2024

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

January 2024 Volume 47, Supplement 1

> [T]he simple word *Care* may suffice to express [the journal's] philosophical mission. The new journal is designed to promote better patient care by serving the expanded needs of all health professionals committed to the care of patients with diabetes. As such, the American Diabetes Association views *Diabetes Care* as a reaffirmation of Francis Weld Peabody's contention that "the secret of the care of the patient is in caring for the patient."
>
> —Norbert Freinkel, *Diabetes Care*, January-February 1978

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Diabetes Care is a journal for the health care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes. To achieve these goals, the journal publishes original research on human studies in the following categories: Clinical Care/Education/Nutrition/Psychosocial Research, Epidemiology/Health Services Research, Emerging Technologies and Therapeutics, Pathophysiology/Complications, and Cardiovascular and Metabolic Risk. The journal also publishes ADA statements, consensus reports, clinically relevant review articles, letters to the editor, and health/medical news or points of view. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other health professionals. More information about the journal can be found online at diabetesjournals.org/care.

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This issue is freely accessible online at https://diabetesjournals.org/care/issue/47/Supplement_1.
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Introduction and Methodology: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S1–S4 | https://doi.org/10.2337/dc24-SINT

Diabetes is a complex, chronic condition requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic management. Ongoing diabetes self-management education and support are critical to empowering people, preventing acute complications, and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The American Diabetes Association (ADA) "Standards of Care in Diabetes," referred to here as the Standards of Care, is intended to provide clinicians, researchers, policy makers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care.

The ADA Professional Practice Committee (PPC) updates the Standards of Care annually and strives to include discussion of emerging clinical considerations in the text, and as evidence evolves, clinical guidance is added to the recommendations in the Standards of Care. The Standards of Care is a "living" document where important updates are published online should the PPC determine that new evidence or regulatory changes (e.g., drug or technology approvals, label changes) merit immediate inclusion. More information on the "Living Standards" can be found on the ADA professional website DiabetesPro at professional.diabetes.org/content-page/living-standards. The Standards of Care supersedes all previously published ADA position statements—and the recommendations therein—on clinical topics within the purview of the Standards of Care; while still containing valuable analysis, ADA position statements should not be considered the current position of the ADA. The Standards of Care receives annual review and approval by the ADA Board of Directors and is reviewed by ADA staff and clinical leadership. The Standards of Care also undergoes external peer review annually.

SCOPE OF THE GUIDELINES

The recommendations in the Standards of Care include screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of people with diabetes. They also cover the prevention, screening, diagnosis, and management of diabetes-associated complications and comorbidities. The recommendations encompass care throughout the life span for youth (children aged birth to 11 years and adolescents aged 12–17 years), adults (aged 18–64 years), and older adults (aged $\geq$65 years). The recommendations cover the management of type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and other types of diabetes and/or hyperglycemic conditions.

The Standards of Care does not provide comprehensive treatment plans for complications associated with diabetes, such as diabetic retinopathy or diabetic foot ulcers, but offers guidance on how and when to screen for diabetes complications, management of complications in the primary care and diabetes care settings, and referral to specialists as appropriate. Similarly, regarding the psychosocial and behavioral health factors often associated with diabetes and that can affect diabetes care, the Standards of Care provides guidance on how and when to screen, management in the primary care and diabetes care settings, and referral but does not provide comprehensive management plans for conditions that require specialized care, such as mental illness.

TARGET AUDIENCE

The target audience for the Standards of Care includes primary care physicians, endocrinologists, nurse practitioners, physician associates/assistants, pharmacists, dietitians, diabetes care and education specialists, and all members of the diabetes care team. The Standards of Care also provides guidance to specialists caring for people with diabetes and its multitude of complications, such as cardiologists, nephrologists, emergency physicians, internists, pediatricians, psychologists, neurologists, ophthalmologists, and podiatrists. Additionally, these recommendations help payers, policy makers, researchers, research funding organizations, and advocacy groups to align their policies and resources and deliver optimal care for people living with diabetes.

The "Standards of Care in Diabetes," formerly called "Standards of Medical Care in Diabetes," was originally approved in 1988. The most recent full review and revision was in December 2023.

**A complete list of members of the American Diabetes Association Professional Practice Committee is provided in this section.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

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The ADA strives to improve and update the Standards of Care to ensure that clinicians, health plans, and policy makers can continue to rely on it as the most authoritative source for current guidelines for diabetes care. The Standards of Care recommendations are not intended to preclude clinical judgment. They must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors. For more detailed information about the management of diabetes, please refer to *Medical Management of Type 1 Diabetes* (1) and *Medical Management of Type 2 Diabetes* (2).

METHODOLOGY AND PROCEDURE

The Standards of Care includes discussion of evidence and clinical practice recommendations intended to optimize care for people with diabetes by assisting health care professionals and individuals in making shared decisions about diabetes care. The recommendations are informed by a systematic review of evidence and an assessment of the benefits and risks of alternative care options.

Professional Practice Committee

The PPC of the ADA is responsible for the Standards of Care. The PPC is an interprofessional expert committee comprising physicians, nurse practitioners, pharmacists, diabetes care and education specialists, registered dietitian nutritionists, behavioral health scientists, and others who have expertise in a range of areas including but not limited to adult and pediatric endocrinology, epidemiology, public health, behavioral health, cardiovascular risk management, microvascular complications, nephrology, neurology, ophthalmology, podiatry, clinical pharmacology, preconception and pregnancy care, weight management and diabetes prevention, and use of technology in diabetes management. Appointment to the PPC is based on excellence in clinical practice and research, with attention to appropriate representation of members based on considerations including but not limited to demographic, geographic, work setting, or identity characteristics (e.g., gender, ethnicity, ability level). A PPC chairperson is appointed by the ADA (currently N.A.E.) and oversees the committee. For the 2024 Standards of Care, as in previous years, two representatives from the American College of Cardiology (ACC) acted as experts and participated in the development of Section 10, “Cardiovascular Disease and Risk Management.” ACC reviewed and approved the section. In addition, and new to the 2024 Standards of Care, one representative from the American Society for Bone and Mineral Research (ASBMR) and one representative from The Obesity Society (TOS) acted as external experts for the “Bone Health” subsection in Section 4, “Comprehensive Medical Evaluation and Assessment of Comorbidities,” and Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes,” respectively. Both societies reviewed and approved the section or subsection in which they were involved.

Each section of the Standards of Care is reviewed annually and updated with the latest evidence-based recommendations by a PPC member designated as the section lead as well as subcommittee members. The subcommittees perform systematic literature reviews and identify and summarize the scientific evidence. An information specialist with knowledge and experience in literature searching (a librarian) is consulted as necessary. A guideline methodologist (R.R.B. for the 2024 Standards of Care) with expertise and training in evidence-based medicine and guideline development methodology oversees all methodological aspects of the development of the Standards of Care and serves as a statistical analyst.

Disclosure and Duality of Interest Management

All members of the expert panel (the PPC members and subject matter experts) and ADA staff are required to comply with the ADA policy on duality of interest, which requires disclosure of any financial, intellectual, or other interests that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. For transparency, ADA requires full disclosure of all relationships. Full disclosure statements from all committee members are solicited and reviewed during the appointment process. Disclosures are then updated throughout the guideline development process (specifically before the start of every meeting), and disclosure statements are submitted by every Standards of Care author upon submission of the revised Standards of Care section. Members are required to disclose for a time frame that includes 1 year prior to initiation of the committee appointment process until publication of that year’s Standards of Care. Potential dualities of interest are evaluated by a designated review group and, if necessary, the Legal Affairs Division of the ADA. The duality of interest assessment is based on the relative weight of the financial relationship (i.e., the monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). In addition, the ADA adheres to section 7 of the Council of Medical Specialty Societies “Code for Interactions with Companies” (3). The duality of interest review group also ensures the majority of the PPC and the PPC chair are without potential conflict relevant to the subject area. Furthermore, the PPC chair is required to remain unconflicted for 1 year after the publication of the Standards of Care. Members of the committee who disclose a potential duality of interest pertinent to any specific recommendation are prohibited from participating in discussions related to those recommendations. No expert panel members were employees of any pharmaceutical or medical device company during the development of the 2024 Standards of Care. Members of the PPC, their employers, and their disclosed potential dualities of interest are listed in the section “Disclosures: *Standards of Care in Diabetes—2024*.” The ADA funds the development of the Standards of Care from general revenue and does not use industry support for this purpose.

Evidence Review

The Standards of Care subcommittee for each section creates an initial list of relevant clinical questions that is reviewed and discussed by the expert panel. In consultation with a systematic review expert, each subcommittee devises and executes systematic literature searches. For the 2024 Standards of Care, PubMed, Medline, and EMBASE were searched for the time periods of 1 June 2022 to 21 July 2023. Searches are limited to studies published in English. Subcommittee members also manually search journals, reference lists of conference proceedings, and regulatory agency websites. All potentially relevant citations are then subjected to a full-text review. In consultation with the methodologist, the subcommittees prepare the evidence summaries and grading for each section of the Standards of Care. All PPC members discuss and review the evidence summaries and make revisions as appropriate. The final evidence summaries are then deliberated on by the PPC, and the recommendations that will appear in the Standards of Care are drafted.

Grading of Evidence and Recommendation Development

A grading system (**Table 1**) developed by the ADA and modeled after existing methods is used to clarify and codify the evidence that forms the basis for the recommendations in the Standards of Care. All of the recommendations in the Standards of Care are critical to comprehensive care regardless of rating. ADA recommendations are assigned ratings of **A**, **B**, or **C**, depending on the quality of the evidence in support of the recommendation. Expert opinion **E** is a separate category for recommendations in which there is no evidence from clinical trials, clinical trials may be impractical, or there is conflicting evidence. Recommendations assigned an **E** level of evidence are informed by key opinion leaders in the field of diabetes (members of the PPC) and cover important elements of clinical care. All Standards of Care recommendations receive a rating for the strength of the evidence and not for the strength of the recommendation. Recommendations with **A**-level evidence are based on large, well-designed randomized controlled trials or well-done meta-analyses of randomized controlled trials. Generally, these recommendations have the best chance of improving outcomes when applied to the population for which they are appropriate. Recommendations with lower levels of evidence may be equally important but are not as well supported.

Of course, published evidence is only one component of clinical decision-making. Clinicians care for people, not populations; guidelines must always be interpreted with the individual person in mind. Individual circumstances, such as comorbid and coexisting diseases, age, education, disability, and, above all, the values and preferences of the person with diabetes, must be considered and may lead to different treatment goals and strategies. Furthermore, conventional evidence hierarchies, such as the one adapted by the ADA, may miss nuances important in diabetes care. For example, although there is excellent evidence from clinical trials supporting the importance of achieving multiple risk factor control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

Table 1—ADA evidence-grading system for "Standards of Care in Diabetes"

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies, including: • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies, including: • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Evidence to Recommendations

All accumulated evidence was reviewed and discussed by all PPC members during virtual meetings and a 2-day in-person meeting in Arlington, Virginia, in July 2023. Standards of Care recommendations were updated based on the newly acquired evidence, and all recommendations were voted on by the PPC, with 80% consensus required for any recommendation to be approved.

Revision Process

Public comment is particularly important in the development of clinical practice recommendations; it promotes transparency and provides key stake holders the opportunity to identify and address gaps in care. The ADA holds a year-long public comment period requesting feedback on the Standards of Care. The PPC reviews compiled feedback from the public in preparation for the annual update but considers more pressing updates throughout the year, which may be published as "living" Standards updates. Feedback from the larger clinical community and general public was invaluable for the revision of the 2023 Standards of Care. Readers who wish to comment on the 2024 Standards of Care are invited to do so at professional.diabetes.org/SOC.

Feedback for the Standards of Care is also obtained from external peer reviewers. The Standards of Care is reviewed by ADA clinical leadership and scientific and medical staff and is approved by the ADA Board of Directors, which includes health care professionals, scientists, and lay people. The ACC performs an independent external peer review and the ACC Board of Directors provides endorsement of Section 10, "Cardiovascular Disease and Risk Management." In addition, the ASBMR Board of Directors provides endorsement for the "Bone Health" subsection of Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," and the TOS Board of Directors provides endorsement for Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes." The ADA adheres to the Council of Medical Specialty Societies revised "CMSS Principles for the Development of Specialty Society Clinical Guidelines" (4).

ADA STANDARDS, STATEMENTS, REPORTS, AND REVIEWS

The ADA has been actively involved in developing and disseminating diabetes care clinical practice recommendations and related documents for more than 30 years. The ADA Standards of Care is an essential resource for health care professionals caring for people with diabetes. ADA Statements, Consensus Reports, and Scientific Reviews support the recommendations included in the Standards of Care.

Standards of Care

The annual Standards of Care supplement to *Diabetes Care* contains the official ADA position, is authored by the ADA, and provides all of the ADA's current clinical practice recommendations.

ADA Statement

An ADA statement is an official ADA point of view or belief that does not contain clinical practice recommendations and may be issued on advocacy, policy, economic, or medical issues related to diabetes. ADA statements undergo a formal review process, including external peer review and review by the appropriate ADA national committee, ADA clinical leadership, science and health care staff, and, as warranted, the ADA Board of Directors.

Consensus Report

A consensus report on a particular topic contains a comprehensive examination, is authored by an expert panel (i.e., consensus panel), and represents the panel's collective analysis, evaluation, and opinion. The need for a consensus report arises when clinicians, scientists, regulators, and/or policy makers desire guidance and/or clarity on a medical or scientific issue related to diabetes for which the evidence is contradictory, emerging, or incomplete. Consensus reports may also highlight evidence gaps and propose future research areas to address these gaps. A consensus report is not an ADA position but represents expert opinion only and is produced under the auspices of the ADA by invited experts. A consensus report may be developed after an ADA Clinical Conference or Research Symposium. Consensus reports undergo a formal review process, including external peer review and review by the appropriate ADA national committee, ADA clinical leadership, and the science and health care staff.

Scientific Review

A scientific review is a balanced review and analysis of the literature on a scientific or medical topic related to diabetes. A scientific review is not an ADA position and does not contain clinical practice recommendations but is produced under the auspices of the ADA by invited experts. The scientific review may provide a scientific rationale for clinical practice recommendations in the Standards of Care. The category may also include task force and expert committee reports.

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Summary of Revisions: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S5–S10 | https://doi.org/10.2337/dc24-SREV

GENERAL CHANGES

The field of diabetes care is rapidly changing as new research, technology, and treatments that can improve the health and well-being of people with diabetes continue to emerge. With annual updates since 1989, the American Diabetes Association (ADA) has long been a leader in producing guidelines that capture the most current state of the field.

The 2024 Standards of Care includes revisions to incorporate person-first and inclusive language. Efforts were made to consistently apply terminology that empowers people with diabetes and recognizes the individual at the center of diabetes care.

Although levels of evidence for several recommendations have been updated, these changes are not outlined below where the clinical recommendation has remained the same. That is, changes in evidence level from, for example, **E** to **C** are not noted below. The 2024 Standards of Care contains, in addition to many minor changes that clarify recommendations or reflect new evidence, more substantive revisions detailed below.

SECTION CHANGES

Section 1. Improving Care and Promoting Health in Populations

(https://doi.org/10.2337/dc24-S001)

Recommendation 1.4 was updated to emphasize improving processes of care and health outcomes, costs, individual preferences and goals, and treatment burden.

The subsection "Status and Demographics of Diabetes Care," formerly "Care Delivery Systems," was updated to include current data with respect to cholesterol, blood pressure, and glycemic management.

The "Cost Considerations for Medication-Taking Behaviors" subsection now includes costs of insulin and glucose monitoring devices, with an update on insulin price lowering.

Language was added to the "Homelessness and Housing Insecurity" subsection to reflect issues more accurately in this population.

The "Social Capital and Community Support" subsection now discusses the possible role of community paramedics in community-based diabetes care.

Section 2. Diagnosis and Classification of Diabetes

(https://doi.org/10.2337/dc24-S002)

The title of Section 2 was changed to "Diagnosis and Classification of Diabetes" to better represent real-world clinical practice (i.e., diagnosis occurs before classification).

Recommendation 2.1a was added to emphasize the structured approach to diagnostic testing, and Recommendation 2.1b was updated to highlight the importance of confirmatory testing when an abnormal test result is identified.

Tables 2.1 and **2.2** were modified to include A1C at the top of the testing hierarchy to acknowledge real-world practice when diagnosing diabetes and prediabetes, respectively.

Recommendation 2.5 was added to emphasize the importance of differentiating which form of diabetes an individual has in order to facilitate personalized management.

Figure 2.1 was added as a new figure to provide a structured framework for investigation of suspected type 1 diabetes in newly diagnosed adults.

The "Type 1 Diabetes" subsection was updated to refine diagnostic criteria for type 1 diabetes based on recent U.S. Food and Drug Administration (FDA) approval of a new drug to delay the incidence of type 1 diabetes. Recommendations 2.6 and 2.7, for type 1 diabetes, were updated accordingly.

Recommendation 2.8 was added for consideration of standardized islet autoantibody tests for classification of diabetes in adults who phenotypically overlap with type 1 diabetes, and a new paragraph was added to highlight the possible association between coronavirus disease 2019 (COVID-19) infection and new-onset type 1 diabetes.

Recommendation 2.15a was added to emphasize the role of several medication classes in increasing the risk of prediabetes and type 2 diabetes and the need for screening.

Recommendation 2.15b was added to provide screening guidance for prediabetes

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*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

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and type 2 diabetes in individuals treated with second-generation antipsychotic medications.

In the “Pancreatic Diabetes or Diabetes in the Context of Disease of the Exocrine Pancreas” subsection, Recommendation 2.17 was added to highlight the importance of screening for diabetes in people following an episode of acute pancreatitis or in individuals with chronic pancreatitis.

In addition, the discussion on cystic fibrosis–related diabetes (CFRD) was incorporated into this subsection. Recommendation 2.19 was modified to clarify that while A1C is not recommended as a screening test for CFRD due to low sensitivity, it is widely used in clinical practice, and a value of ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD.

Section 3. Prevention or Delay of Diabetes and Associated Comorbidities

(https://doi.org/10.2337/dc24-S003)

Recommendation 3.2 was added to state the importance of monitoring individuals at risk for developing type 1 diabetes, as a younger age of seroconversion (particularly under age 3 years), the number of diabetes-related autoantibodies identified, and the development of autoantibodies against islet antigen 2 (IA-2) have all been associated with more rapid progression to clinical type 1 diabetes.

Recommendation 3.15 was added to address use of teplizumab, which was approved to delay the onset of stage 3 type 1 diabetes in adults and pediatric individuals (aged 8 years and older) with stage 2 type 1 diabetes.

Section 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

(https://doi.org/10.2337/dc24-S004)

In Recommendation 4.1, language was modified to be more inclusive for comprehensive medical evaluation.

Figure 4.1 was updated to include individual lifestyle choices when choosing treatment, and **Table 4.1** was modified to include changes made throughout Section 4.

Changes were made in the “Immunizations” subsection to reflect the COVID-19 post-pandemic period, and updates were made regarding the respiratory syncytial virus vaccine in adults ≥60 years of age with chronic conditions such as diabetes. **Table 4.4**, formerly **Table 4.5**, was revised to include these important vaccination updates.

The subsection on "Bone Health" has been extensively revised and updated to reflect the current best practices in the field. Recommendations 4.9–4.14 were added to include regular evaluation and treatment for bone health, and accompanying text was expanded to reflect these updates. **Table 4.5** was added to include general and diabetes-specific risk factors for fracture.

Recommendation 4.22 was added to include assessment and referral to appropriate health care professionals who specialize in disability management, which was expanded upon in the text.

Major changes regarding liver disease in people with diabetes were previously added as a 2023 Living Standards update, with extensive recommendations for screening and management to be in alignment with other professional societies. In addition, the recently proposed changes in the nomenclature proposed for steatotic liver disease is discussed. The terminology for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis was maintained at this time.

The “Bone Health” subsection is endorsed by the American Society for Bone and Mineral Research.

Section 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes

(https://doi.org/10.2337/dc24-S005)

The recommendations and text of Section 5 were adjusted to place focus on guiding the behavior of health care professionals rather than people with diabetes, thus aligning with the purpose of the Standards of Care as guidance for health care professionals.

Recommendation 5.2 was updated to reflect five critical times to evaluate the need for diabetes self-management and education (DSMES): at diagnosis, when not meeting treatment goals, annually, when complicating factors develop, and when transitions in life and care occur.

Recommendation 5.4 was updated to include a broader integration of cultural sensitivity in the context of person-centered care.

Recommendation 5.5 reflects inclusion of telehealth and digital interventions for DSMES.

The “Diabetes Self-Management Education and Support” subsection text was updated to reflect changes in DSMES reimbursement policies and the importance of addressing barriers to using DSMES services.

Recommendation 5.13 was added to the “Medical Nutrition Therapy” subsection to incorporate inclusive food-based eating patterns with key nutrition principles that are foundational to all people with diabetes, and Recommendation 5.20 was updated to emphasize including healthy fats within the context of a Mediterranean style of eating.

A subsection on religious fasting was added, and the concept of chrononutrition (impact of eating on circadian rhythms) was introduced.

Recommendation 5.23 was updated to include advising alcohol abstainers to not begin use of alcohol for the purpose of improving health outcomes.

The text on nonnutritive sweeteners was expanded to address the World Health Organization’s conditional recommendation on their use and safety.

In the “Physical Activity” subsection, Recommendation 5.31 was updated to define sedentary behavior and to be inclusive of all types of diabetes. The text of this subsection was updated to include a discussion of the application and benefits of high-intensity interval training.

The subsection “Smoking Cessation: Tobacco, E-cigarettes, and Cannabis” was updated to include cannabis. Although not enough data are available to support a new recommendation, the text of this subsection was revised to include a discussion on cannabis use. In addition, Recommendation 5.33 was updated to advise that clinicians ask people with diabetes about use of cigarettes or other tobacco products and make appropriate referrals for cessation as a routine component of diabetes care and education.

Recommendation 5.36 in the “Psychosocial Care” subsection was updated to provide greater detail for psychosocial screening protocols, including diabetes-related mood concerns, stress, and quality of life.

Recommendation 5.39 was changed to specify the frequency for diabetes distress screening and to highlight the role of health care professionals in addressing diabetes distress. The accompanying text also includes links to validated measures of diabetes distress.

Recommendation 5.40 has been updated to include screening for fear of hypoglycemia.

Recommendation 5.41 has been updated to reflect increased frequency for depression screening and monitoring in people with a history of depression.

In the "Sleep Health" subsection, Recommendation 5.51 was added to recommend practicing sleep-promoting routines and habits.

Section 6. Glycemic Goals and Hypoglycemia

(https://doi.org/10.2337/dc24-S006)

The title of Section 6 was changed to "Glycemic Goals and Hypoglycemia," and hypoglycemia content throughout the Standards of Care was consolidated into this section.

Recommendation 6.1 was updated to include more frequent glycemic assessment for populations needing closer glycemic monitoring.

The "Glycemic Assessment by A1C" subsection was revised to reflect recent data on the strengths and limitations of the A1C assay and to include a discussion of the benefits and limitations of serum glycated protein assays as alternatives to A1C.

Table 6.2 was updated to outline CGM metrics and recommended glycemic goals.

The subsections "Glucose Lowering and Microvascular Complications" and "Glucose Lowering and Cardiovascular Disease Outcomes" were updated to include evidence on long-term follow-up of clinical trials of tight glycemic management and to put these findings into the context of newer diabetes medications with cardiovascular and renal benefits.

Recommendations 6.8a and 6.8b were added to clarify the clinical scenarios where deintensifying diabetes medications is appropriate, and text in the "Setting and Modifying Glycemic Goals" subsection was added to discuss the rationale for this update.

Recommendations 6.11a, 6.11b, and 6.11c were added to clarify when and how health care professionals should review an individual's hypoglycemia history, awareness, and risk. **Table 6.5**, which provides a summary of hypoglycemia risk factors (formerly in Section 4), was updated to reflect recent evidence. The "Hypoglycemia Risk Assessment" subsection was added to provide the background and rationale for **Table 6.5**.

Several recommendations were added to and updated within the "Hypoglycemia Assessment, Prevention, and Treatment" subsection. Recommendation 6.11d was added to highlight the benefits of continuous glucose monitoring (CGM) use for hypoglycemia prevention. Recommendation 6.12 was revised to provide hypoglycemia treatment guidance inclusive of individuals using automated insulin delivery (AID) systems, and details were added to the text. Recommendation 6.13 was revised to clarify criteria for prescribing glucagon and express preference for glucagon preparations that do not have to be reconstituted. **Table 6.6** was added to summarize currently available glucagon products and their monthly costs. Recommendation 6.14 was added to address the need for patient education for hypoglycemia prevention and treatment, especially for insulin users. Recommendations 6.15 and 6.16 were updated to communicate how hypoglycemic events should inform modification of the diabetes treatment plan and to direct clinicians to use evidence-based interventions to reestablish awareness of hypoglycemia, respectively.

Table 6.7 was added to summarize the components of hypoglycemia prevention and their recommended frequency.

Section 7. Diabetes Technology

(https://doi.org/10.2337/dc24-S007)

Recommendation 7.1 was added to state that people with diabetes should be offered any type of diabetes device (e.g., insulin pens, connected pens, glucose meters, and CGM or AID systems), and Recommendation 7.2 was added to emphasize the need to start CGM early in type 1 diabetes, even at diagnosis, to promote early achievement of glycemic goals.

Recommendation 7.3 was added to emphasize that health care professionals should acquire sufficient knowledge for the use and application of diabetes technology for people with diabetes, and the text has been expanded to discuss the need for both knowledge and competency for interprofessional teams managing diabetes care.

Recommendation 7.8 was modified to align with Section 14, "Children and Adolescents," to support initiation of an insulin pump and/or AID system early for individuals with type 1 diabetes, even at diagnosis.

Recommendation 7.15 was updated to reflect the benefits of intermittently scanned CGM in less intensively treated people with type 2 diabetes.

The text on CGM systems was expanded to include updates on systems that are cleared for integration with AID systems and to include the benefits of CGM use in type 2 diabetes for those using nonintensive insulin therapy and/or not using insulin therapy. In addition, the text was updated to include suggestions to streamline the approach to CGM interpretation by various methods, such as assessing data sufficiency and reviewing glycemic trends to modify therapeutic approaches.

The text on real-time CGM was updated to outline the systems that can be used by pregnant individuals with diabetes, and substances that interfere with CGM device accuracy were updated in the text and in **Table 7.4**.

Recommendation 7.24 was refined to emphasize the usefulness of insulin pens or insulin injection aids for people with dexterity issues or vision impairment.

The text on AID systems was updated to include benefits reported from real-world studies.

Recommendation 7.33 was added to emphasize continuation of personal CGM use in hospitalized individuals with diabetes when clinically appropriate in a hybrid fashion and under an institutional protocol.

Section 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

(https://doi.org/10.2337/dc24-S008)

Language throughout the section was amended to be person centered and to emphasize the importance of weight management within the overall context of the treatment of people with diabetes, and the justification for a weight-based approach to diabetes treatment has been expanded. The recommendations and text pertaining to weight management treatment have been expanded to acknowledge the expected range of benefits across the spectrum of weight loss.

Recommendations 8.2a, 8.2b, and 8.3 were expanded to incorporate additional anthropometric measurements beyond BMI (i.e., waist circumference, waist-to-hip ratio, and/or waist-to-height ratio) to encourage individualized assessments of body fat mass and distribution.

Recommendation 8.6 was added to highlight that approaches to treating obesity should be individualized and that any of the established approaches (i.e., intensive behavioral interventions, pharmacologic treatment, or metabolic surgery) can be considered in people with obesity and diabetes alone or in combination.

Recommendation 8.8b was updated to suggest counseling strategies to address barriers to access.

Recommendations 8.11a and 8.11b were updated to highlight the effectiveness of weight maintenance programs and to suggest monitoring weight loss progress while providing ongoing support for maintaining goals long term.

Recommendation 8.17 was added to include glucagon-like peptide 1 (GLP-1) receptor agonists or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist with greater weight loss efficacy as preferred pharmacotherapy for obesity management in people with diabetes.

Recommendation 8.18 was added to address the importance of reevaluation for obesity treatment intensification or deintensification for people with diabetes to reach their weight goals.

The text of the "Metabolic Surgery" subsection was updated to emphasize preventing and addressing therapeutic inertia pertaining to weight management goals in people with obesity and type 2 diabetes.

Recommendation 8.19 was updated in response to growing evidence of the long-term benefits of metabolic surgery treatment in people with obesity and type 2 diabetes.

Recommendation 8.20 now includes a link to accredited metabolic and bariatric surgery centers.

Recommendation 8.25 was added to emphasize the importance of monitoring weight loss progress of individuals who have undergone metabolic surgery. In the case of inadequate progress, potential barriers and additional weight loss interventions should be considered.

Table 8.1 was updated to include the recent FDA approvals and price changes for several obesity pharmacotherapies.

This section is endorsed by The Obesity Society.

Section 9. Pharmacologic Approaches to Glycemic Treatment

(https://doi.org/10.2337/dc24-S009)

Recommendation 9.2 was updated to reflect preference of insulin analogs or inhaled insulin over injectable human insulins to minimize hypoglycemia risk for most adults with type 1 diabetes.

Recommendation 9.3 was added to include early use of CGM for adults with type 1 diabetes, and Recommendation 9.4 was added to indicate consideration for use of AID systems for adults with type 1 diabetes.

Recommendation 9.5 was expanded to include educating adults with type 1 diabetes on how to modify their insulin dose based on concurrent glycemia, glycemic trends, and sick day management.

Recommendation 9.6 was added to suggest prescribing glucagon for individuals taking insulin or at high risk for hypoglycemia.

Recommendation 9.7 was added to emphasize the importance of regular treatment plan evaluation for individuals with diabetes to ensure individualized goals are met.

Recommendation 9.14 was updated to highlight the importance of early combination therapy when shortening the time to attainment of individualized treatment goals for adults with type 2 diabetes.

Recommendation 9.15 was added to reflect that pharmacologic therapies should address both individualized glycemic and weight goals in adults with type 2 diabetes without cardiovascular and/or kidney disease.

Recommendation 9.16 was added to advise consideration of additional glucose-lowering agents for adults with type 2 diabetes not meeting their individualized glycemic goals.

Recommendation 9.17 was added to highlight the importance of treatment intensification and combination of approaches pertaining to weight management and their alignment with glycemic management goals for adults with type 2 diabetes.

Recommendation 9.18 was updated to reflect prioritizing glycemic management agents that also reduce cardiovascular and kidney disease risk in adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease.

For adults with type 2 diabetes who have heart failure, Recommendation 9.19 was added to recommend sodium–glucose cotransporter 2 (SGLT2) inhibitors for glycemic management and prevention of heart failure hospitalizations.

Recommendations 9.20 and 9.21 were added to reflect individualized recommendations for individuals with type 2 diabetes and chronic kidney disease.

Recommendation 9.22 was updated to reflect that insulin therapy should be considered at any stage irrespective of other glucose-lowering medications in certain circumstances.

Recommendation 9.23 was updated to include a dual GIP and GLP-1 receptor agonist as an additional option for greater glycemic management that is preferred to insulin, and Recommendation 9.24 was updated to reflect reassessing insulin dosing upon addition or dose escalation of a GLP-1 receptor agonist or a dual GIP and GLP-1 receptor agonist.

Recommendation 9.25 was broadened to include any glucose-lowering agents if justified for additional benefits (e.g., weight management, cardiometabolic, or kidney benefits) to treatment goals.

Recommendation 9.26 was added to suggest reassessing the need and/or dosages for other glucose-lowering agents that are associated with higher risk of hypoglycemia when initiating or intensifying insulin treatment.

Recommendations 9.28 and 9.29 were added to provide guiding principles of care for people with obstacles that may impede their diabetes management.

Figure 9.1 was updated to reflect a terminology change from "hybrid closed-loop technology" to "automated insulin delivery systems."

Table 9.1 was updated to reflect terminology updates, and **Table 9.2** was updated to include counseling people with diabetes about potential for ileus (subcutaneous semaglutide) and to include that dual GIP and GLP-1 receptor agonist treatment is not recommended for individuals with a history of gastroparesis.

Tables 9.3 and **9.4** were updated to reflect changes in cost for several agents.

Section 10. Cardiovascular Disease and Risk Management

(https://doi.org/10.2337/dc24-S010)

Recommendation 10.12 was revised to recommend monitoring of serum creatinine/estimated glomerular filtration rate and potassium within 7–14 days after initiation of treatment with an ACE inhibitor, angiotensin receptor blocker, mineralocorticoid receptor agonist, or diuretic.

Recommendation 10.24 was added to include bempedoic acid treatment for people with diabetes and without established cardiovascular disease who are intolerant to statin therapy. In addition, Recommendation 10.28b recommends bempedoic acid or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy with monoclonal antibody treatment or inclisiran siRNA as alternative cholesterol-lowering therapy. A new subsection, “Intolerance to Statin Therapy,” was added to expand on these updates.

Recommendation 10.35b has been modified to recommend an interprofessional team approach that includes a cardiovascular or neurological specialist to decide on the length of treatment with dual antiplatelet therapy in people with diabetes after an acute coronary syndrome or ischemic stroke/transient ischemic attack.

Recommendations 10.39a and 10.39b were added to include screening of adults with diabetes for asymptomatic heart failure by measuring a natriuretic peptide level to facilitate the prevention or progression to symptomatic stages of heart failure.

Recommendation 10.40 was modified to include screening for peripheral artery disease with ankle-brachial index testing in asymptomatic people with diabetes aged ≥50 years , microvascular disease in any location, foot complications, or any end-organ damage from diabetes. Peripheral artery disease screening should be considered for individuals with diabetes for ≥10 years or more.

Recommendation 10.42a was updated to recommend either an SGLT2 inhibitor or an SGLT1/2 inhibitor for people with diabetes and established heart failure with preserved or reduced ejection fraction to reduce risk of worsening heart failure and cardiovascular death. Additional text includes a discussion on cardiovascular outcomes trials of the SGLT1/2 inhibitor sotagliflozin.

Recommendations 10.45a–10.45e have been added to address treatment approaches for people with diabetes and heart failure, including the roles of an interprofessional team and pharmacological approaches to prevent heart failure progression and hospitalization.

Recommendation 10.47 was added to suggest including education on risks and signs of ketoacidosis and methods of management and tools for testing in people with type 1 diabetes, ketosis-prone type 2 diabetes, and/or those consuming ketogenic diets treated with SGLT inhibition.

Figure 10.2 was modified to reflect changes in initial blood pressure values and treatment recommendations for confirmed hypertension in nonpregnant people with diabetes.

This section is endorsed by the American College of Cardiology.

Section 11. Chronic Kidney Disease and Risk Management

(https://doi.org/10.2337/dc24-S011)

Section 11 was updated to align with the latest consensus report on diabetes management in chronic kidney disease by the ADA and Kidney Disease: Improving Global Outcomes (KDIGO).

Recommendation 11.4a was updated to include the role of ACE inhibitors or angiotensin receptor blockers in preventing the progression of kidney disease and reducing cardiovascular events.

Recommendation 11.7 was updated to reflect dietary protein intake levels for individuals with stage 3 or higher chronic kidney disease who are currently treated with dialysis.

Figure 11.1 was updated and illustrates chronic kidney disease progression, frequency of visits, and referral to nephrology according to glomerular filtration rate and albuminuria. **Figure 11.2** was added to present a holistic approach for improving outcomes in individuals with diabetes and chronic kidney disease.

Section 12. Retinopathy, Neuropathy, and Foot Care

(https://doi.org/10.2337/dc24-S012)

Language in Recommendations 12.1, 12.2, 12.5, and 12.7 was refined to be more actionable by health care professionals.

Recommendation 12.6 was updated to indicate the application of FDA-approved artificial intelligence algorithms, and the text was updated with approved artificial intelligence algorithm details and clinical trials.

Recommendations 12.15 and 12.16 were added to address vision loss from diabetes, and the text was expanded to discuss complications of vision loss and the importance of evaluation and rehabilitation.

The text in the “Neuropathy” subsection was updated to discuss the limited data available to support use of lidocaine 5% plaster/patch and gastric stimulation as efficacious therapies for people with diabetes.

In the "Foot Care" subsection, Recommendation 12.27 was updated to include toe pressures when screening for peripheral artery disease. In addition, Recommendation 12.28 was amended to include the importance of an interprofessional approach facilitated by a podiatrist with other appropriate team members for individuals who have foot ulcers and high-risk feet (e.g., individuals on dialysis, with Charcot foot, with prior ulcer or amputation history, or with peripheral artery disease).

Table 12.2 was updated to include “Fish skin graft” under “Acellular matrix tissues” for advanced wound therapies.

Section 13. Older Adults

(https://doi.org/10.2337/dc24-S013)

Recommendation 13.6 was modified to align with the revised Medicare reimbursement rules allowing CGM for adults with type 2 diabetes on any insulin.

Recommendations 13.8a, 13.8b, and 13.8c were amended to highlight the heterogeneity present for treatment goals for older adults, especially those with intermediate or complex health conditions who need to personalize glycemic goals.

Recommendations 13.16a–13.16d were updated to highlight the need to deintensify therapy, most particularly hypoglycemia-causing medications (such as insulin, sulfonylureas, and meglitinides). These recommendations also suggest switching to classes of glucose-lowering medications with a lower risk of hypoglycemia to meet individualized glycemic goals. In addition, treatment plans for older adults with diabetes and other comorbidities (e.g., atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease) should include agents that reduce cardiorenal risk, regardless of glycemia.

Section 14. Children and Adolescents

(https://doi.org/10.2337/dc24-S014)

Recommendation 14.4 was added to state the need for insulin dosing adjustments according to meal composition.

In the “Psychosocial Care” subsection, Recommendation 14.10 was revised to include screening details for psychosocial and behavioral health concerns and for appropriate referral when indicated, and Recommendation 14.12 was updated to clarify diabetes distress and lower engagement in diabetes self-management behavior.

Recommendation 14.53 was modified to state “at least” a 7–10% decrease in excess weight for youth with overweight and obesity with type 2 diabetes when recommending developmentally and culturally appropriate comprehensive lifestyle programs.

Recommendations 14.68 and 14.70 were updated to include consideration for empagliflozin prior to initiating and/or intensifying insulin therapy plans for glycemic management, and **Fig. 14.1** was updated to include empagliflozin.

Recommendation 14.69 was added to suggest consideration for medication-taking behavior and the medications' effects on weight for youth with overweight or obesity and type 2 diabetes.

The term "severe obesity" in Recommendation 14.72 was changed to "class 2 obesity or higher (BMI >35 kg/m^2 or 120% of 95th percentile for age and sex, whichever is lower)" to provide greater details for adolescents being considered for metabolic surgery.

Recommendation 14.78 was updated to clarify protein intake according to age for those with nephropathy.

The new subsection "Substance Use in Pediatric Diabetes" includes Recommendations 14.106 and 14.107 to discourage initiation of smoking (tobacco and electronic cigarettes) and to encourage smoking cessation. The text was expanded to discuss the adverse health effects of smoking and exposure to secondhand smoke for youth with diabetes.

In the "Transition from Pediatric to Adult Care" subsection, Recommendations 14.108 and 14.109 were revised to reflect the role of interprofessional teams in the transition from pediatric to adult care and to be more person centered. Recommendation 14.110 was added to give direction for the coordination between pediatric diabetes specialists and youth with diabetes and their caregivers on the timing of transfer to adult care.

Section 15. Management of Diabetes in Pregnancy

(https://doi.org/10.2337/dc24-S015)

"Reproductive potential" was changed to "childbearing potential" throughout the section to be more specific. "Women" was changed to "individuals" throughout the section, except for instances mentioning the title of a published study, to be more inclusive.

In the "Preconception Care" subsection, Recommendation 15.4 was updated to highlight the approach of interprofessional care and the need for inclusion of an endocrinology health care professional, and Recommendation 15.5 was expanded to include physical activity for preconception care.

In the "Glycemic Goals in Pregnancy" subsection, Recommendation 15.7 was modified to emphasize that all pregnant individuals with diabetes should monitor fasting, preprandial, and postprandial blood glucose levels, and Recommendation 15.10 was updated to include CGM use for pregnant individuals with type 1 diabetes.

The text in "Insulin Physiology" was expanded to include information about changes to basal and bolus insulin requirements as pregnancy progresses for individuals with preexisting diabetes.

The text in "Glucose Monitoring" was updated to differentiate lower limits of glucose thresholds based on blood and sensor glucose monitoring.

Language was added to "Continuous Glucose Monitoring in Pregnancy" to encourage individualization for CGM use in pregnant individuals with type 2 diabetes or gestational diabetes mellitus (GDM). Language was also added to clarify the international consensus on time in range for pregnant individuals with type 2 diabetes or GDM.

Recommendation 15.15 was updated to clarify that metformin and glyburide, individually or in combination, should not be used as first-line agents for treating hyperglycemia in pregnancy.

Language was added to the "Preeclampsia and Aspirin" subsection to note that individuals with GDM may also be candidates for aspirin therapy if they have a single high risk factor or multiple moderate risk factors.

Recommendation 15.27 was updated to encourage breastfeeding efforts for all individuals with diabetes who are postpartum.

The "Postpartum Care" subsection was updated to explain that a preconception evaluation is needed for individuals with childbearing potential who have prediabetes or a history of GDM.

Section 16. Diabetes Care in the Hospital

(https://doi.org/10.2337/dc24-S016)

Recommendation 16.2 was expanded to emphasize the need for personalized approaches in the emergency department, intensive care unit and nonintensive care unit wards, gynecology-obstetrics/delivery units, dialysis suites, and psychiatric wards. The text has been expanded to encourage institutions to perform regular audits to monitor proper use of protocols and to ensure institute educational/training programs keep staff up to date.

Recommendation 16.4 was updated to reflect that insulin and other therapies should be initiated or intensified for treatment of persistent hyperglycemia starting at a threshold of 180 mg/dL (10.0 mmol/L).

Recommendation 16.5a was added to delineate the glycemic goals for most critically ill individuals with hyperglycemia (target glucose range of 140–180 mg/dL [7.8–10.0 mmol/L]), and Recommendation 16.5b was updated to suggest more stringent goals (110–140 mg/dL [6.1–7.8 mmol/L]) for selected critically ill individuals if these goals can be achieved without significant hypoglycemia.

Recommendations 16.6 and 16.7 were added to indicate continued use of personal CGM devices and use of AID systems in conjunction with CGM, respectively, in the inpatient setting if clinically appropriate, with confirmatory point-of-care glucose measurements for insulin dosing decisions and hypoglycemia assessment, if resources and training are available, and according to an institutional protocol. The narrative has also been expanded to recommend a personalized approach for achieving glycemic goals throughout the hospital stay.

In the "Perioperative Care" subsection, a statement was added about the safe use of GLP-1 receptor agonists in the perioperative period.

The "Glucose-Lowering Treatment in Hospitalized Patients" subsection discusses the evidence on the coadministration of a low dose of basal insulin analog while on intravenous insulin infusion.

For the management of diabetic ketoacidosis and hyperglycemic hyperosmolar state, the text has been expanded to include a nurse-driven protocol with a variable rate based on glucose values as an option.

Recommendation 16.11 was added to indicate the use of SGLT2 inhibitors for individuals with type 2 diabetes hospitalized with heart failure during hospitalization and that SGLT2 inhibitors should be continued after recovery from acute illness if no contraindications are present.

Section 17. Diabetes Advocacy

(https://doi.org/10.2337/dc24-S017)

The Care of Young Children With Diabetes in the Childcare and Community Setting advocacy statement has been updated.

1. Improving Care and Promoting Health in Populations: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S11–S19 | https://doi.org/10.2337/dc24-S001

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at https://professional.diabetes.org/SOC.

DIABETES AND POPULATION HEALTH

Recommendations

1.1 Ensure treatment decisions are timely, rely on evidence-based guidelines, capture key elements within the social determinants of health, and are made collaboratively with people with diabetes and care partners based on individual preferences, prognoses, comorbidities, and informed financial considerations. **B**

1.2 Align approaches to diabetes management with the Chronic Care Model. This model emphasizes person-centered team care, integrated long-term treatment approaches to diabetes and comorbidities, and ongoing collaborative communication and goal setting between all team members. **A**

1.3 Care systems should facilitate in-person and virtual team-based care, include those knowledgeable and experienced in diabetes management as part of the team, and utilize patient registries, decision support tools, and community involvement to meet needs of individuals with diabetes. **B**

1.4 Assess diabetes health care maintenance (**Table 4.1**) using reliable and relevant data metrics to improve processes of care and health outcomes, with attention to care costs, individual preferences and goals for care, and treatment burden. **B**

Population health is defined as "the health outcomes of a group of individuals, including the distribution of health outcomes within the group"; these outcomes can be measured in terms of health outcomes (mortality, morbidity, and functional status), disease burden (incidence and prevalence), and behavioral and metabolic factors (physical activity, nutrition, A1C, etc.) (1). Clinical practice recommendations for health care professionals are tools that can ultimately improve health across populations; however, for optimal outcomes, diabetes care must also be individualized for each person with diabetes and across their life span. Thus, efforts to improve population health will require a combination of policy-level, system-level, and

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**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

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person-level approaches. With such an integrated approach in mind, the American Diabetes Association (ADA) highlights the importance of person-centered care, defined as care that considers an individual's comorbidities and prognoses; is respectful of and responsive to individual preferences, needs, and values; and ensures that the individual's values guide all clinical decisions (2). Furthermore, wider social determinants of health (SDOH)—often out of direct control of the individual and potentially representing lifelong risk—contribute to health care and psychosocial outcomes and must be addressed to improve all health outcomes (3). Clinical practice recommendations, whether based on evidence or expert opinion, are intended to guide an overall approach to care. The science and art of health care come together when the clinician makes treatment decisions for a person who may not meet the eligibility criteria used in the studies on which guidelines are based. Recognizing that one size does not fit all, the standards presented here provide guidance for when and how to adapt recommendations for an individual. This section provides guidance for health care professionals as well as health systems, payers, and policymakers.

Status and Demographics of Diabetes Care

The proportion of people with diabetes who achieve recommended A1C, blood pressure, and LDL cholesterol levels has fluctuated over the years, with some improvement over time (4). Glycemic management and management of cholesterol through dietary intake remain challenging. In 2015–2018, just 50.5% of U.S. community-dwelling adults with diabetes achieved A1C $<$7% and 75.4% achieved A1C $<$8%. The goal blood pressure of $<$130/80 mmHg was achieved by just 47.7% adults with diabetes, while 70.4% achieved blood pressure $<$140/90 mmHg. Lipid control, then defined as non-HDL cholesterol $<$130 mg/dL, was achieved by 55.7% adults with diabetes, and all three risk factors were controlled by just 22.2%. Importantly, many people who did not attain A1C, blood pressure, and lipid goals are not receiving any or adequate pharmacotherapy for glycemic, hypertension, and dyslipidemia management, respectively, which underscores the vital and urgent need for care delivery systems to engage and support people living with diabetes. Certain segments of the population, such as young adults and individuals with complex comorbidities, financial or other social hardships, and/or limited English proficiency, as well as individuals in ethnic minority populations, face particular challenges to goal-based care (5–7). A U.S. population–based study based on the National Health and Nutrition Examination Survey (NHANES) showed that younger people with diabetes, individuals who are Mexican American or non-Hispanic Black, those with lower level of educational attainment, and those who are underinsured are most likely to be undertreated, particularly for glycemic control (4). The persistent variability in the quality of diabetes care across health care professionals and practice settings indicates that substantial system-level improvements are still needed.

Diabetes and its associated health complications pose a significant financial burden to individuals and society. It is estimated that the annual cost of diagnosed diabetes in the U.S. in 2022 was $413 billion, including $307 billion in direct health care costs and $106 billion in reduced productivity. After adjusting for inflation, the economic costs of diabetes increased by 7% between 2017 and 2022 and by 35% from 2012 to 2022 (8). This is attributed to the increased prevalence of diabetes and the increased cost per person with diabetes. People living with diabetes also face financial hardship, which is correlated with higher A1C, diabetes distress, and depressive symptoms (9). Therefore, ongoing population health strategies like the Chronic Care Model (CCM) are needed to reduce costs to the health care system and to people with diabetes and to provide optimized care.

Chronic Care Model

Numerous interventions to promote the recommended standards have been implemented. However, a major barrier to optimal care is a delivery system that is often fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the coordinated delivery of chronic care. The CCM is a commonly used framework for describing diabetes care programs (10).

Six Core Elements. The CCM includes six core elements to optimize the care of people with chronic disease:

1. Delivery system design (moving from a reactive to a proactive care delivery system where planned visits are coordinated through a team-based approach)
2. Self-management support
3. Decision support, particularly at the point of care during a clinical encounter (basing care on evidence-based, effective care guidelines)
4. Clinical information systems (using registries that can provide person-specific and population-based support to the care team)
5. Community resources and policies (identifying or developing resources to support healthy lifestyles)
6. Health systems (to create a quality-oriented culture)

A 5-year effectiveness study of the CCM in 53,436 people with type 2 diabetes in the primary care setting suggested that the use of this model of care delivery reduced the cumulative incidence of diabetes-related complications and all-cause mortality (11). Individuals who were enrolled in the CCM experienced a reduction in cardiovascular disease risk by 56.6%, microvascular complications by 11.9%, and mortality by 66.1% (11). In addition, another study suggested that health care utilization was lower in the CCM group, which resulted in health care savings of $7,294 per individual over the study period (12).

Redefining the roles of the health care delivery team and empowering self-management of people with diabetes are fundamental to the successful implementation of the CCM (13). Collaborative, interprofessional teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate individuals' self-management (14–16). There are references to guide the implementation of the CCM into diabetes care delivery, including opportunities and challenges (17).

Strategies for System-Level Improvement

Optimal diabetes management requires an organized, systematic approach and the involvement of a coordinated team of dedicated health care professionals working in an environment where person-centered, high-quality care is a priority (7,17–19). While many diabetes care processes have improved nationally in the past decade, the overall quality of care for people with diabetes remains suboptimal (4). Efforts to increase the quality of diabetes care include providing care that is concordant with evidence-based guidelines (20); expanding the role of teams to implement more intensive disease management strategies (7,16,21,22); tracking medication-taking behavior at a systems level (23); redesigning the organization of the care process (24); implementing electronic health record (EHR) tools (25,26); empowering and educating people with diabetes (27,28); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, diabetes technology, and essential medications (7,29); leveraging telehealth capabilities to improve access to care (30); assessing and addressing psychosocial issues (31,32); and identifying, developing, and engaging community resources and public policies that support healthy lifestyles (33). The National Diabetes Education Program maintains an online resource (cdc.gov/diabetes/professional-info/training.html) to help health care professionals design and implement more effective health care delivery systems for those with diabetes. Given the pluralistic needs of people with diabetes and that the constant challenges they experience vary over the course of disease management (complex insulin treatment plans, new technology, etc.), a diverse team with complementary expertise is consistently recommended (34).

Care Teams

The care team, which centers around the person with diabetes, should avoid therapeutic inertia and prioritize timely and appropriate intensification of behavior change (nutrition and physical activity) and/or pharmacologic therapy for individuals who have not achieved the recommended metabolic goals (35–37). Strategies shown to improve care team behavior and thereby catalyze reductions in A1C, blood pressure, and/or LDL cholesterol include engaging in explicit and collaborative goal setting with people with diabetes (38,39); integrating evidence-based guidelines and clinical information tools into the process of care (20,40,41); identifying and addressing language, numeracy, or cultural barriers to care (41–43); soliciting performance feedback, setting reminders, and providing structured care (e.g., guidelines, formal case management, and patient education resources) (7); and incorporating care management teams including nurses, dietitians, pharmacists, and other health care professionals (21,42). In addition, initiatives such as the Patient-Centered Medical Home can improve health outcomes by fostering comprehensive primary care and offering new opportunities for team-based chronic disease management (43,44).

Telehealth

Telehealth is a growing field that may increase access to care for people with diabetes. The American Telemedicine Association defines telemedicine as the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telehealth includes a growing variety of applications and services using two-way video, smartphones, wireless tools, and other forms of telecommunications technology (45). Often used interchangeably with telemedicine, telehealth describes a broader range of digital health services in health care delivery (46). This includes synchronous, asynchronous, and remote patient monitoring.

Telehealth should be used complementary to in-person visits to optimize glycemic management in people with unmanaged diabetes (47). Increasingly, evidence suggests that various telehealth modalities may facilitate reducing A1C in people with type 2 diabetes compared with usual care or in addition to usual care (48), and findings suggest that telemedicine is a safe method of delivering care for people with type 1 diabetes in rural areas (49). For rural populations or those with limited physical access to health care, telemedicine has a growing body of evidence for its effectiveness, particularly with regard to glycemic management as measured by A1C (30,50–52). In addition, evidence supports the effectiveness of telehealth in diabetes, hypertension, and dyslipidemia interventions (53) as well as the telehealth delivery of motivational interviewing (54). Interactive strategies that facilitate communication between health care professionals and people with diabetes, including the use of web-based portals or text messaging and those that incorporate medication adjustment, appear more effective. Telehealth and other virtual environments can also be used to offer diabetes self-management education and clinical support and remove geographic and transportation barriers for individuals living in under-resourced areas or with disabilities (55). Telehealth resources can also have a role in addressing the SDOH in young adults with diabetes (56). However, limited data are available on the effectiveness across different populations (57).

Behaviors and Well-being

Successful diabetes care also requires a systematic approach to supporting the behavior-change efforts of people with diabetes. High-quality diabetes self-management education and support (DSMES) has been shown to improve patient self-management, satisfaction, and glucose outcomes. National DSMES standards call for an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem-solving), and engagement with psychosocial concerns. Increasingly, such support is being adapted for online platforms that have the potential to promote patient access to this important resource. These curriculums need to be tailored to the needs of the intended populations, including addressing the "digital divide," i.e., access to the technology required for implementation (58–61).

For more information on DSMES, see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes."

Cost Considerations for Medication-Taking Behaviors

The cost of diabetes medications and devices is an ongoing barrier to achieving glycemic goals. Up to 25% of people with diabetes who are prescribed insulin report cost-related insulin underuse (62). Insulin underuse due to cost has also been termed "cost-related medication non-adherence" (here referred to as cost-related barriers to medication use). There are recommendations from the ADA Insulin Access and Affordability Working Group for approaches to this issue from a systems level (63). Recommendations including concepts such as cost-sharing for insured people with diabetes should be based on the lowest price available, the list price for insulins that closely reflects the net price, and health plans that ensure people with diabetes can access insulin without undue administrative burden or excessive cost (63). In 2023, three major insulin manufacturers lowered the prices of insulin, which may help reduce the financial burden of diabetes management, although costs for insulin delivery and glucose monitoring remain high. People with diabetes should be screened for financial burden of treatment, cost-related barriers to medication use, and rationing of other essential services due to medical costs (64).

The cost of medications (not only insulin) influences prescribing patterns and medication use because of burden on the person with diabetes and lack of secondary payer support (public and private insurance) for effective approved glucose-lowering, cardiovascular disease risk-reducing, and weight management therapeutics. Financial barriers remain a major source of health disparities, and costs should be a focus of treatment goals (65). (See TAILORING TREATMENT FOR SOCIAL CONTEXT and TREATMENT CONSIDERATIONS.) Reduction in cost-related barriers to medication use is associated with better biologic and psychologic outcomes, including quality of life (66).

Access to Care and Quality Improvement

The Affordable Care Act and Medicaid expansion have increased access to care for many individuals with diabetes, emphasizing the protection of people with preexisting conditions, health promotion, and disease prevention (67). In fact, health insurance coverage increased from 84.7% in 2009 to 90.1% in 2016 for adults with diabetes aged 18–64 years. As of early 2022, more than 35 million people in the U.S. were enrolled in some form of Affordable Care Act–related health insurance (68). Coverage for those aged ≥65 years remained nearly universal (69). People with diabetes who have either private or public insurance coverage are more likely to meet quality indicators for diabetes care (70). As mandated by the Affordable Care Act, the Agency for Healthcare Research and Quality developed a National Quality Strategy based on triple aims that include improving the health of a population, overall quality and patient experience of care, and per capita cost (71,72). As health care systems and practices adapt to the changing landscape of health care, it will be important to integrate traditional disease-specific metrics with measures of patient experience, as well as cost, in assessing the quality of diabetes care (73,74). Information and guidance specific to quality improvement and practice transformation for diabetes care are available from the National Institute of Diabetes and Digestive and Kidney Diseases guidance on diabetes care and quality (75) Using patient registries and EHRs, health systems can evaluate the quality of diabetes care being delivered and perform intervention cycles as part of quality improvement strategies (76). Improvement of health literacy and numeracy is also a necessary component to improve care (77,78). Critical to these efforts is health professional adherence to clinical practice recommendations (**Table 4.1**) and the use of accurate, reliable data metrics that include sociodemographic variables to examine health equity within and across populations (79).

In addition to quality improvement efforts, other strategies that simultaneously improve the quality of care and potentially reduce costs are gaining momentum and include reimbursement structures that, in contrast to visit-based billing, reward the provision of appropriate and high-quality care to achieve metabolic goals (80), value-based payments, and incentives that accommodate personalized care goals (7,81). (Also see COST CONSIDERATIONS FOR MEDICATION-TAKING BEHAVIORS, above, regarding cost-related barriers to medication use.)

TAILORING TREATMENT FOR SOCIAL CONTEXT

Recommendations

1.5 Assess food insecurity, housing insecurity/homelessness, financial barriers, and social capital/social community support to inform treatment decisions, with referral to appropriate local community resources. **A**

1.6 Provide people with diabetes with additional self-management support from lay health coaches, navigators, or community health workers when available. **A**

1.7 Consider the involvement of community health workers to support the management of diabetes and cardiovascular risk factors, especially in underserved communities and health care systems. **B**

Health inequities related to diabetes and its complications are well documented, are heavily influenced by SDOH, and have been associated with greater risk for diabetes, higher population prevalence, and poorer diabetes outcomes (82–86). SDOH are defined as the economic, environmental, political, and social conditions in which people live and are responsible for a major part of health inequality worldwide (87). Greater exposure to adverse SDOH over the life course results in poor health (88). The ADA recognizes the association between social and environmental factors and the prevention and treatment of diabetes and has issued a call for research that seeks to better understand how social determinants influence behaviors and how the relationships between these variables might be modified for the prevention and management of diabetes (89,90). While a comprehensive strategy to reduce diabetes-related health inequities in populations has not been formally studied, general recommendations from other chronic disease management and prevention models can be drawn upon to inform systems-level strategies in diabetes (91). For example, the National Academy of Medicine has published a framework for educating health care professionals on the importance of SDOH (92). Furthermore, there are resources available for the inclusion of standardized sociodemographic variables in EHRs to facilitate the measurement of health inequities and the impact of interventions designed to reduce those inequities (74,92,93).

SDOH are not consistently recognized and often go undiscussed in the clinical encounter (85). Among people with chronic illnesses, two-thirds of those who reported not taking medications as prescribed due to cost-related barriers to medication use never shared this with their physician (94). A study using data from the National Health Interview Survey (NHIS) (85) found that one-half of adults with diabetes reported financial stress and one-fifth reported food insecurity. A Canadian study noted an association of one or more adverse SDOH and health care utilization and poor diabetes outcomes in high-risk children with type 1 diabetes (94). It is therefore important for people with diabetes to be screened for SDOH during clinical encounters and be referred to appropriate clinical and community resources to address these needs. Health systems may benefit from compiling an inventory of such resources to facilitate referrals at the point of care. Policies and payment models that support addressing SDOH, both within and outside the health care setting, are needed to ensure that these efforts are both feasible and sustainable. One example of a statewide payment model that incentivizes value-based care, addressing SDOH and-funding community-based health care professionals, is the Maryland Total Cost of Care Model, although it is currently limited by a narrow focus such as preventing diabetes rather than overall diabetes care quality (95,96).

Another population in which such issues must be considered is older adults, for whom social difficulties may impair quality of life and increase the risk of functional dependency (97) (see Section 13, "Older Adults," for a detailed discussion of social considerations in older adults). Creating systems-level mechanisms to screen for SDOH may help overcome structural barriers and communication gaps between people with diabetes and health care professionals (85,98). Pilot studies have proven the effectiveness of identifying SDOH by using validated screening tools (99). In addition, brief, validated screening tools for some SDOH exist and could facilitate discussion around factors that significantly impact treatment during the clinical encounter. Below is a discussion of assessment and treatment considerations in the context of food insecurity, homelessness, limited English proficiency, limited health literacy, and low literacy.

Food Insecurity

Food insecurity is the unreliable availability of nutritious food and the inability to consistently obtain food without resorting to socially unacceptable practices. Over 18% of the U.S. population reported food insecurity between 2005 and 2014 (100). The rate is higher in some racial and ethnic minority groups, including African American and Latino populations, low-income households, and homes headed by single mothers. The food insecurity rate in individuals with diabetes may be up to 20% (101). Additionally, the risk for type 2 diabetes is increased twofold in those with food insecurity (89) and has been associated with lower engagement in self-care behaviors and medication use, depression, diabetes distress, and worse glycemic management when compared with individuals who are food secure (102–104). Older adults with food insecurity are more likely to have emergency department visits and hospitalizations compared with older adults who do not report food insecurity (105). Risk for food insecurity can be assessed with a validated two-item screening tool (106) that includes the following statements: *1*) "Within the past 12 months, we worried whether our food would run out before we got money to buy more" and *2*) "Within the past 12 months the food we bought just didn't last, and we didn't have money to get more." An affirmative response to either statement had a sensitivity of 97% and specificity of 83%. Interventions such as food prescription programs are considered promising to address food insecurity by integrating community resources into primary care settings and directly dealing with food deserts in underserved communities (107,108).

Treatment Considerations

In those with diabetes and food insecurity, the priority is mitigating the increased risk for uncontrolled hyperglycemia and severe hypoglycemia. The reasons for the increased risk of hyperglycemia include the steady consumption of inexpensive carbohydrate-rich processed foods, binge eating, financial constraints to filling diabetes medication prescriptions, and anxiety and depression leading to poor diabetes self-care behaviors. Hypoglycemia can occur due to inadequate or erratic carbohydrate consumption following the administration of sulfonylureas or insulin. See **Tables 9.2–9.4** for drug-specific and patient factors, including cost and risk of hypoglycemia, which may be important considerations for adults with food insecurity and type 2 diabetes. Health care professionals should consider these factors when making treatment decisions for people with food insecurity and seek local resources to help people with diabetes and their family members obtain nutritious food more regularly (109).

Homelessness and Housing Insecurity

Homelessness and housing insecurity often accompany other barriers that limit diabetes self-management. Food insecurity, lack of insurance, cognitive impairment, behavioral health deficiencies, and low literacy and numeracy skills are also factors (110). The prevalence of diabetes in the homeless population is estimated to be around 8% (111). Additionally, people with diabetes who are homeless need secure places to keep their diabetes supplies and refrigerator access to properly store their insulin and take it on a regular schedule. The risk for homelessness can be ascertained using a brief risk assessment tool developed and validated for use among veterans (112). Housing insecurity has also been shown to be directly associated with a person's ability to maintain their diabetes self-management (113). Given the potential challenges, health care professionals who care for either homeless or housing-insecure individuals should be familiar with resources or have access to social workers who can facilitate stable housing for these individuals as a way to improve diabetes care (114).

Migrant and Seasonal Agricultural Workers

Migrant and seasonal agricultural workers may have a higher risk of type 2 diabetes than the overall population. While migrant farmworker–specific data are lacking, most agricultural workers in the U.S. are Latino, a population with a high rate of type 2 diabetes. In addition, living in severe poverty brings with it food in-security, high chronic stress, and an increased risk of diabetes; there is also an association between the use of certain pesticides and the incidence of diabetes (115).

Data from the Department of Labor indicate that there are 2.5–3 million agricultural workers in the U.S. These agricultural workers travel throughout the country, serving as the backbone for a multibillion-dollar agricultural industry. According to 2021 health center data, 175 health centers across the U.S. reported that they provided health care services to 893,260 adult agricultural patients, and 91,124 had encounters for diabetes (10.2%) (116).

Migrant farmworkers encounter numerous and overlapping barriers to receiving care. Migration, which may occur as frequently as every few weeks for farmworkers, disrupts care. In addition, cultural and linguistic barriers, lack of transportation and money, lack of available work hours, unfamiliarity with new communities, lack of access to resources, and other barriers prevent migrant farmworkers from accessing health care. Without regular care, those with diabetes may suffer severe and often expensive complications that affect quality of life. Nontraditional care delivery models, including mobile integrated health and telehealth, can be leveraged to improve access to high quality care.

Health care professionals should be attuned to all patients' working and living conditions. For example, if a migrant farmworker with diabetes presents for care, appropriate referrals should be initiated to social workers and community resources, as available, to assist with removing barriers to care.

Language Barriers

Health care professionals who care for non–English speakers should develop or offer educational programs and materials in culturally adaptive languages specific to these individuals with the specific goals of preventing diabetes and building diabetes awareness in people who cannot easily read or write in English. The National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (National CLAS Standards) provide guidance on how health care professionals can reduce language barriers by improving their cultural competency, addressing health literacy, and ensuring communication with language assistance (117). In addition, the National CLAS Standards website offers several resources and materials that can be used to improve the quality of care delivery to non–English-speaking individuals (117).

Health Literacy and Numeracy

Health literacy is defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate decisions (77). Health literacy is strongly associated with patients engaging in complex disease management and self-care (118). Approximately 80 million adults in the U.S. are estimated to have limited or low health literacy (78). Clinicians and diabetes care and education specialists should ensure they provide easy-to-understand information and reduce unnecessary complexity when developing care plans with people with diabetes. Interventions addressing low health literacy in populations with diabetes seem effective in improving diabetes outcomes, including ones focusing primarily on patient education, self-care training, or disease management. Combining easily adapted materials with formal diabetes education demonstrates effectiveness on clinical and behavioral outcomes in populations with low literacy (119). However, evidence supporting these strategies is largely limited to observational studies. More research is needed to investigate the most effective strategies for enhancing both acquisition and retention of diabetes knowledge and examine different media and strategies for delivering interventions to people with diabetes (120).

Health numeracy is also essential in diabetes prevention and management. Health numeracy requires primary numeric skills, applied health numeracy, and interpretive health numeracy. An emotional component also affects a person's ability to understand concepts of risk, probability, and communication of scientific evidence (121). People with prediabetes or diabetes often need to perform numeric tasks such as interpreting food labels and blood glucose levels to make treatment decisions such as medication dosing. Thus, both health literacy and numeracy are necessary for enabling effective communication between people with diabetes and health professionals, arriving at a treatment plan, and making diabetes self-management task decisions. If people with diabetes appear not to understand concepts associated with treatment decisions, both can be assessed using standardized screening measures (122). Adjunctive education and support may be indicated if limited health literacy and numeracy are barriers to optimal care decisions (31).

Social Capital and Community Support

Social capital, which comprises community and personal network instrumental support, promotes better health, whereas lack of social support is associated with poorer health outcomes in individuals with diabetes (90). Of particular concern are the SDOH, including racism and discrimination, which are likely to be lifelong (123). These factors are rarely addressed in routine treatment or disease management but may be underlying reasons for lower engagement in self-care behaviors and medication use. Community resources are recognized by the CCM as a core component of chronic care management (10), with a particular need to incorporate relevant social support networks. There is currently a paucity of evidence regarding enhancing these resources for those most likely to benefit from such intervention strategies.

Health care community linkages are receiving increasing attention from the American Medical Association, the Agency for Healthcare Research and Quality, and others to promote the translation of clinical recommendations for nutrition and physical activity in real-world settings (124). Community health workers (CHWs) (125), community paramedics (126), peer supporters (127–129), and lay leaders (130) may assist in the delivery of DSMES services (92,131), particularly in underserved communities. The American Public Health Association defines a CHW as a "frontline public health worker who is a trusted member of and/or has an unusually close understanding of the community served" (132). CHWs can be part of a cost-effective, evidence-based strategy to improve the management of diabetes and cardiovascular risk factors in underserved communities and health care systems (133). The CHW scope of practice in areas such as outreach and communication, advocacy, social support, basic health education, referrals to community clinics, and other services has successfully provided social and primary preventive services to underserved populations in rural and hard-to-reach communities. Even though CHWs' core competencies are not clinical in nature, in some circumstances, clinicians may delegate limited clinical tasks to CHWs. If such is the case, these tasks must always be performed under the direction and supervision of the delegating health professional and following state health care laws and statutes (134,135). Community paramedics are advanced paramedics with training in chronic disease monitoring and education, medication management, care coordination, and SDOH in addition to their emergency medical services expertise. While their scope of practice varies across states, community paramedics can engage and support people living with diabetes under the direction of a medical director by delivering diabetes education, assisting with medication management, performing health assessments and wound care, and connecting people with diabetes and care partners with clinical and community resources (126).

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2. Diagnosis and Classification of Diabetes: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is both underutilized as an energy source and overproduced due to inappropriate gluconeogenesis and glycogenolysis, resulting in hyperglycemia (1). Diabetes can be diagnosed by demonstrating increased concentrations of glucose in venous plasma or increased A1C in the blood. Diabetes is classified conventionally into several clinical categories (e.g., type 1 or type 2 diabetes, gestational diabetes mellitus, and other specific types derived from other causes, such as genetic causes, exocrine pancreatic disorders, and medications) (2).

DIAGNOSTIC TESTS FOR DIABETES

Recommendations

2.1a Diagnose diabetes based on A1C or plasma glucose criteria, either the fasting plasma glucose (FPG) value, 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or random glucose value accompanied by classic hyperglycemic symptoms/crises criteria (**Table 2.1**). **A**

2.1b In the absence of unequivocal hyperglycemia (e.g., hyperglycemic crises), diagnosis requires confirmatory testing (**Table 2.1**). **A**

Diabetes may be diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose (FPG) value, 2-h glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or random glucose value accompanied by classic hyperglycemic symptoms (e.g., polyuria, polydipsia, and unexplained weight loss) or hyperglycemic crises (**Table 2.1**).

FPG, 2-h PG during 75-g OGTT, and A1C are appropriate for diagnostic screening. It should be noted that detection rates of different screening tests vary in both populations and individuals. FPG, 2-h PG, and A1C reflect different aspects of glucose metabolism, and diagnostic cut points for the different tests will identify different groups

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**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., A1C and FPG) or at two different time points.

of people (3). Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes (4). Moreover, the efficacy of interventions for primary prevention of type 2 diabetes has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria (5–8).

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (9) (**Table 2.1** and **Table 2.2**). Diabetes may be identified anywhere along the spectrum of clinical scenarios—in seemingly low-risk individuals who happen to have glucose testing, in individuals screened based on diabetes risk assessment, and in symptomatic individuals. There is presently insufficient evidence to support the use of continuous glucose monitoring (CGM) for screening or diagnosis of prediabetes or diabetes. For additional details on the evidence used to establish the criteria for the diagnosis of diabetes, prediabetes, and abnormal glucose tolerance (IFG and IGT), see the American Diabetes Asso-ciation (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (2) and other reports (3,10,11).

Use of Fasting Plasma Glucose or 2-Hour Plasma Glucose for Screening and Diagnosis of Diabetes

In the less common clinical scenario where a person has classic hyperglycemic symptoms (e.g., polyuria, polydipsia, and unexplained weight loss), measurement of random plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus random plasma glucose ≥200 mg/dL [≥11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Health care professionals may also want to know the A1C to determine the chronicity of hyperglycemia.

In an individual without symptoms, FPG or 2-h PG can be used for screening and diagnosis of diabetes. In nonpregnant individuals, FPG (or A1C) is typically preferred for routine screening due to the ease of administration; however, the 2-h PG (OGTT) testing protocol may identify individuals with diabetes who may otherwise be missed (e.g., those with cystic fibrosis–related diabetes or posttransplantation diabetes mellitus). In the absence of classic hyperglycemic symptoms, repeat testing is required to confirm the diagnosis regardless of the test used (see CONFIRMING THE DIAGNOSIS, below).

An advantage of glucose testing is that these assays are inexpensive and widely available. Disadvantages include the high diurnal variation in glucose and fasting requirement. Individuals may have difficulty fasting for the full 8-h period or may misreport their fasting status. Recent physical activity, illness, or acute stress can also affect glucose concentrations. Glycolysis is also an important and underrecognized concern with glucose testing. Glucose concentrations will be falsely low if samples are not processed promptly or stored properly prior to analysis (1).

People should consume a mixed diet with at least 150 g of carbohydrates on the 3 days prior to OGTT (12–14). Fasting and carbohydrate restriction can falsely elevate glucose level with an oral glucose challenge.

Use of A1C for Screening and Diagnosis of Diabetes

Recommendations

2.2a The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) as traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. **B**

2.2b Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to U.S. Food and Drug Administration–approved devices at Clinical Laboratory Improvement Amendments (CLIA)–certified laboratories that perform testing of moderate complexity or higher by trained personnel. **B**

2.3 Marked discordance between A1C and repeat blood glucose values should raise the possibility of a problem or interference with either test. **B**

Table 2.2—Criteria defining prediabetes in nonpregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

2.4 In conditions associated with an altered relationship between A1C and glycemia, such as some hemoglobin variants, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, plasma glucose criteria should be used to diagnose diabetes. **B**

The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) (ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Point-of-care A1C assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic control in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)–regulated and CLIA-waived settings. FDA-approved point-of-care A1C testing can be used in laboratories or sites that are CLIA certified, are inspected, and meet the CLIA quality standards. These standards include specified personnel requirements (including documented annual competency assessments) and participation three times per year in an approved proficiency testing program (15–18).

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and fewer day-to-day perturbations during stress, changes in nutrition, or illness. However, it should be noted that there is lower sensitivity of A1C at the designated cut point compared with that of glucose tests as well as greater cost and limited access in some parts of the world.

A1C reflects glucose bound to hemoglobin over the life span of the erythrocyte (∼120 days) and is thus a “weighted” average that is more heavily affected by recent blood glucose exposure. This means that clinically meaningful changes in A1C can be seen in <120 days. A1C is an indirect measure of glucose exposure, and factors that affect hemoglobin concentrations or erythrocyte turnover can affect A1C (e.g., thalassemia or folate deficiency). A1C may not be a suitable diagnostic test in people with anemia, people treated with erythropoietin, or people undergoing hemodialysis or HIV treatment (19,20). Some hemoglobin variants can interfere with A1C test results, but this depends on the specific assay. For individuals with a hemoglobin variant but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from hemoglobin variants should be used. An updated list of A1C assays with interferences is available at ngsp.org/interf.asp. Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals in the U.S., is associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with levels in individuals without the variant (21).

There is controversy regarding racial differences in A1C. Studies have found that African American individuals have slightly higher A1C levels than non-Hispanic White or Hispanic people (22–25). The glucose-independent racial difference in A1C is small (∼0.3 percentage points) and may reflect genetic differences in hemoglobin or red cell turnover that vary by ancestry. There is an emerging understanding of the genetic determinants of A1C (21), but the field lacks adequate genetic data in diverse populations (26,27). While some genetic variants might be more common in certain race or ancestry groups, it is important that we do not use race or ancestry as proxies for poorly understood genetic differences. Reassuringly, studies have shown that the association of A1C with risk for complications appears to be similar in African American and non-Hispanic White populations (28).

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., individual with classic symptoms of hyperglycemia or hyperglycemic crisis and random plasma glucose ≥200 mg/dL [≥11.1 mmol/L]), diagnosis requires two abnormal screening test results, measured either at the same time (29) or at two different time points. If using samples at two different time points, it is recommended that the second test, which may be either a repeat of the initial test or a different test, be performed promptly. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. Two different tests (such as A1C and FPG) both having results above the diagnostic threshold when collected at the same time or at two different time points would also confirm the diagnosis. On the other hand, if an individual has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of factors that may affect measured A1C or glucose levels. The diagnosis is made based on the confirmatory screening test. For example, if an individual meets the diabetes criterion of A1C (two results ≥6.5% [≥48 mmol/mol]) but not FPG (<126 mg/dL [<7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

If individuals have test results near the margins of the diagnostic threshold, the health care professional should educate the individual about the onset of possible hyperglycemic symptoms and repeat the test in 3–6 months.

Consistent and substantial discordance between glucose and A1C test results should prompt additional follow-up to determine the underlying reason for the discrepancy and whether it has clinical implications for the individual. In addition, consider other biomarkers, such as fructosamine and glycated albumin, which are alternative measures of chronic hyperglycemia that are approved for clinical use for monitoring glycemic control in people with diabetes.

CLASSIFICATION

Recommendation

2.5 Classify people with hyperglycemia into appropriate diagnostic categories to aid in personalized management. **E**

Diabetes is classified conventionally into several clinical categories, although these are being reconsidered based on genetic, metabolomic, and other characteristics and pathophysiology (2):

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adults)
2. Type 2 diabetes (due to a non-autoimmune progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance and metabolic syndrome)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine

   pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of people with HIV, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes).

*This section reviews most common forms of diabetes but is not comprehensive. For additional information, see the ADA position statement "Diagnosis and Classification of Diabetes Mellitus" (*2*).*

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining personalized therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are not accurate, as both diseases occur in all age-groups. Children with type 1 diabetes often present with the hallmark symptoms of polyuria/polydipsia, and approximately half present with diabetic ketoacidosis (DKA) (30–32). The onset of type 1 diabetes may be more variable in adults; they may not present with the classic symptoms seen in children and may experience temporary remission from the need for anticipated full-dose insulin replacement (33–35). The features most useful in discrimination of type 1 diabetes include younger age at diagnosis ($<$35 years) with lower BMI ($<$25 kg/m^2), unintentional weight loss, ketoacidosis, and plasma glucose $>$360 mg/dL ($>$20 mmol/L) at presentation (36) (**Fig. 2.1**). Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history, or a history of autoimmune diseases, are weak discriminators. Occasionally, people with type 2 diabetes may present with DKA (37,38), particularly members of certain racial and ethnic groups (e.g., African American adults, who may present with ketosis-prone type 2 diabetes) (39).

It is important for health care professionals to realize that classification of diabetes type is not always straightforward at presentation and that misdiagnosis is common and can occur in $\sim$40% of adults with new type 1 diabetes (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes and individuals with maturity-onset diabetes of the young [MODY] misdiagnosed as having type 1 diabetes) (36). Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the diagnosis becomes more obvious over time in people with β-cell deficiency as the degree of β-cell deficiency becomes clear (**Fig. 2.1**). One useful clinical tool for distinguishing diabetes type is the **AABBCC** approach: Age (e.g., for individuals $<$35 years old, consider type 1 diabetes); Autoimmunity (e.g., personal or family history of autoimmune disease or polyglandular autoimmune syndromes); Body habitus (e.g., BMI $<$25 kg/m^2); Background (e.g., family history of type 1 diabetes); Control (e.g., level of glucose control on noninsulin therapies); and Comorbidities (e.g., treatment with immune checkpoint inhibitors for cancer can cause acute autoimmune type 1 diabetes) (36).

In both type 1 and type 2 diabetes, genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will be informed by better characterization of the many paths to β-cell demise or dysfunction (40). Across the globe, many groups are working on combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes that are currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing personalized treatment approaches (41).

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is clear from prospective studies that the persistent presence of two or more islet autoantibodies is a near-certain predictor of clinical diabetes (42). In at-risk cohorts followed from birth or a very young age, seroconversion rarely occurs before 6 months of age and there is a peak in seroconversion between 9 and 24 months of age (43–45). The rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels may rise well before the clinical onset of diabetes (e.g., changes in FPG and 2-h PG can occur about 6 months before diagnosis) (46), making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes have been defined (**Table 2.3**) and serve as a framework for research and regulatory decision-making (40,47).

There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or type 1 diabetes. The clinical priority with detection of LADA is awareness that slow autoimmune β-cell destruction can occur in adults, leading to a long duration of marginal insulin secretory capacity. For this classification, all forms of diabetes mediated by autoimmune β-cell destruction independent of age of onset are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to have progressive autoimmune β-cell destruction (48), thus accelerating insulin initiation prior to deterioration of glucose management or development of DKA (34,49). At the same time, there is evidence that application of only a single imperfect autoantibody test for determining LADA classification may lead to misclassification of some individuals with type 2 diabetes. Diagnostic accuracy may be improved by utilizing higher-specificity tests, confirmatory testing for other autoantibodies, and restricting testing to those with clinical features suggestive of autoimmune diabetes (50).

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β-cell insulin secretion, frequently in the setting of insulin resistance, appears to be the common denominator. Type 2 diabetes is associated with insulin secretory defects related to genetic predisposition, epigenetic changes, inflammation, and metabolic stress. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction (40,51–54).

Table 2.3—Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

Adapted from Skyler et al. (40). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials (79).

TYPE 1 DIABETES

Recommendations

2.6 Screening for presymptomatic type 1 diabetes may be done by detection of autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2), or zinc transporter 8 (ZnT8). **B**

2.7 Having multiple confirmed islet autoantibodies is a risk factor for clinical diabetes. Testing for dysglycemia may be used to further forecast near-term risk. When multiple islet autoantibodies are identified, referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay development of clinical diabetes should be considered. **B**

2.8 Standardized islet autoantibody tests are recommended for classification of diabetes in adults who have phenotypic risk factors that overlap with those for type 1 diabetes (e.g., younger age at diagnosis, unintentional weight loss, ketoacidosis, or short time to insulin treatment). **E**

Immune-Mediated Diabetes

Autoimmune type 1 diabetes accounts for 5–10% of diabetes and is caused by autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to glutamic acid decarboxylase (GAD) (such as GAD65), insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2β, and zinc transporter 8 (ZnT8). Numerous clinical studies are being conducted to test various methods of preventing or delaying type 1 diabetes in those with evidence of islet autoimmunity (trialnet.org/our-research/prevention-studies) (42–44,49,55,56). The disease has strong HLA associations, with linkage to the *DQB1* and *DRB1* haplotypes, and genetic screening has been used in some research studies to identify high-risk populations. Specific alleles in these genes can be either predisposing (e.g., DRB1*0301-DQB1*0201 [DR3-DQ2] and DRB1*0401-DQB1*0302 [DR4-DQ8]) or protective (e.g., DRB1*1501 and DQA1*0102-DQB1*0602). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoantibodies and normoglycemia. At stage 1, the 5-year risk of developing symptomatic type 1 diabetes is ∼44% overall but varies considerably based on number, titer, and specificity of autoantibodies as well as age of seroconversion and genetic risk (47). Stage 2 includes individuals with multiple islet autoantibodies and dysglycemia. At stage 2 of the disease, there is ∼60% risk by 2 years and ∼75% risk within 5 years of developing symptomatic type 1 diabetes (57,58).

The rate of β-cell destruction is quite variable, being rapid in some individuals (particularly but not exclusively in infants and children) and slow in others (mainly but not exclusively adults) (46,59). Children and adolescents often present with DKA as the first manifestation of the disease, and rates in the U.S. have increased dramatically over the past 20 years (30–32). Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress. Adults may retain sufficient β-cell function to prevent DKA for many years; such individuals may have remission or decreased insulin needs for months or years, eventually become dependent on insulin for survival, and are at risk for DKA (33–35,60,61). At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age.

Autoimmune destruction of β-cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. Although individuals do not typically have obesity when they present with type 1 diabetes, obesity is increasingly common in the general population; as such, obesity should not preclude testing for type 1 diabetes. People with type 1 diabetes are also prone to other autoimmune disorders, such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"). Type 1 diabetes can be associated with monogenic polyglandular autoimmune syndromes, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is an early-onset systemic autoimmune, genetic disorder caused by mutation of the forkhead box protein 3 (*FOXP3*) gene, and another disorder caused by the autoimmune regulator (*AIRE*) gene mutation (62,63).

Introduction of immunotherapy, specifically checkpoint inhibitors, for cancer treatment has led to unexpected adverse events, including immune system activation precipitating autoimmune disease. Fulminant onset of type 1 diabetes can occur, with DKA and low or undetectable levels of C-peptide as a marker of endogenous β-cell function (64–66). Fewer than

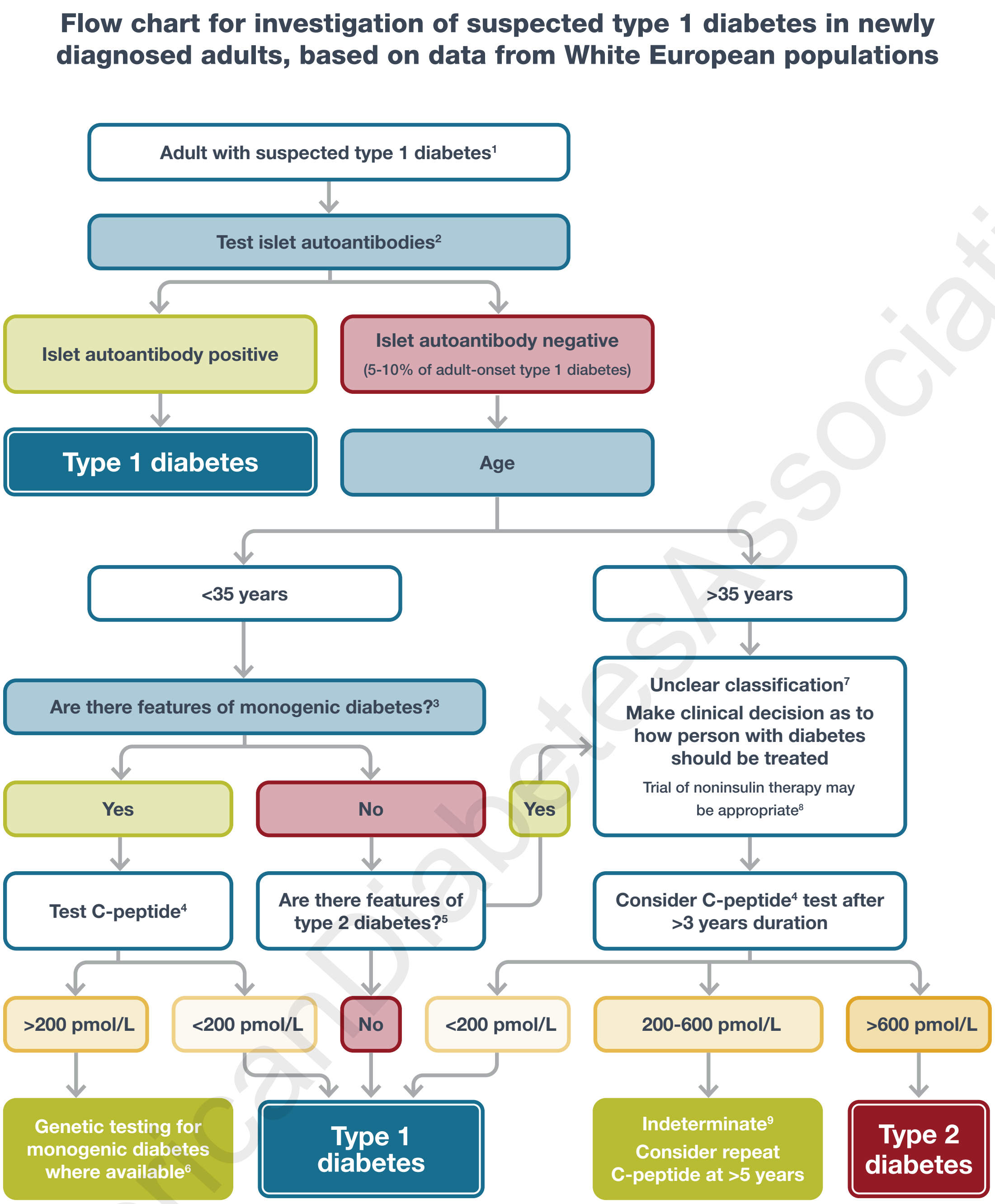

Flow chart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations
Adult with suspected type 1 diabetes[1]
Test islet autoantibodies[2]
Islet autoantibody positive
Islet autoantibody negative
(5-10% of adult-onset type 1 diabetes)
Type 1 diabetes
Age
<35 years
>35 years
Are there features of monogenic diabetes?[3]
Unclear classification[7]
Make clinical decision as to how person with diabetes should be treated
Trial of noninsulin therapy may be appropriate[8]
Yes
No
Yes
Test C-peptide[4]
Are there features of type 2 diabetes?[5]
Consider C-peptide[4] test after >3 years duration
>200 pmol/L
<200 pmol/L
No
<200 pmol/L
200-600 pmol/L
>600 pmol/L
Genetic testing for monogenic diabetes where available[6]
Type 1 diabetes
Indeterminate[9]
Consider repeat C-peptide at >5 years
Type 2 diabetes

Figure 2.1—Flowchart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations. [1]No single clinical feature confirms type 1 diabetes in isolation. [2]Glutamic acid decarboxylase (GAD) should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA-2) and/or zinc transporter 8 (ZnT8) where these tests are available. In individuals who have not been treated with insulin, antibodies against insulin may also be useful. In those diagnosed at <35 years of age who have no clinical features of type 2 diabetes or monogenic diabetes, a negative result does not change the diagnosis of type 1 diabetes, since 5–10% of people with type 1 diabetes do not have antibodies. [3]Monogenic diabetes is suggested by the presence of one or more of the following features: A1C <58 mmol/mol (<7.5%) at diagnosis, one parent with diabetes, features of a specific monogenic cause (e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, and severe insulin resistance in the absence of obesity), and monogenic diabetes prediction model probability >5% (diabetesgenes.org/exeter-diabetes-app/ModyCalculator). [4]A C-peptide test is only indicated in people receiving insulin treatment. A random sample (with concurrent glucose) within 5 h of eating can replace a formal C-peptide stimulation test in the context of classification. If the result is ≥600 pmol/L (≥1.8 ng/mL), the circumstances of testing do not matter. If the result is <600 pmol/L (<1.8 ng/mL) and the concurrent glucose is <4 mmol/L (<70 mg/dL) or the person may have been fasting, consider repeating the test. Results showing very low levels (e.g., <80 pmol/L [<0.24 ng/mL]) do not need to be repeated. Where a person is insulin treated, C-peptide must be measured prior to insulin discontinuation to exclude severe insulin deficiency. Do not test C-peptide within 2 weeks of a hyperglycemic emergency. [5]Features of type 2 diabetes include increased BMI (≥25 kg/m^2), absence of weight loss, absence of ketoacidosis, and less marked hyperglycemia. Less discriminatory features include non-White ethnicity, family history, longer duration and milder severity of symptoms prior to presentation, features of the metabolic syndrome, and absence of a family history of autoimmunity. [6]If genetic testing does not confirm monogenic diabetes, the classification is unclear and a clinical decision should be made about treatment. [7]Type 2 diabetes should be strongly considered in older individuals. In some cases, investigation for pancreatic or other types of diabetes may be appropriate. [8]A person with possible type 1 diabetes who is not treated with insulin will require careful monitoring and education so that insulin can be rapidly initiated in the event of glycemic deterioration. [9]C-peptide values 200–600 pmol/L (0.6–1.8 ng/mL) are usually consistent with type 1 diabetes or maturity-onset diabetes of the young but may occur in insulin-treated type 2 diabetes, particularly in people with normal or low BMI or after long duration. Reprinted and adapted from Holt et al. (36).

half of these individuals have autoantibodies that are seen in type 1 diabetes, supporting alternate pathobiology. This immune-related adverse event occurs in just under 1% of checkpoint inhibitor–treated individuals but most commonly occurs with agents that block the programmed cell death protein 1/programmed cell death ligand 1 pathway alone or in combination with other checkpoint inhibitors (67). To date, the majority of immune checkpoint inhibitor–related cases of type 1 diabetes occur in people with high-risk HLA-DR4 (present in 76% of individuals), whereas other high-risk HLA alleles are not more common than those in the general population (67). To date, risk cannot be predicted by family history or autoantibodies, so all health care professionals administering these medications or caring for people who have a history of current or past exposure to these agents should be mindful of this adverse effect and educate and monitor individuals appropriately.

A number of viruses have been associated with type 1 diabetes, including enteroviruses such as Coxsackievirus B. During the coronavirus disease 2019 (COVID-19) pandemic, cases of hyperglycemia, DKA, and new diabetes increased, suggesting that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a trigger for or can unmask type 1 diabetes (68). Possible mechanisms of β-cell damage include virus-triggered β-cell death, immune-mediated loss of pancreatic β-cells, and damage to β-cells because of infection of surrounding exocrine cells. The cytokine storm associated with COVID-19 infection is a highly inflammatory state that could also contribute. To better characterize and understand the pathogenesis of new-onset COVID-19–related diabetes, a global registry, CoviDIAB, has been established (69).

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. Individuals have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity. However, only a minority of people with type 1 diabetes fall into this category.

Individuals with autoantibody-negative diabetes of African or Asian ancestry may suffer from episodic DKA and exhibit varying degrees of insulin deficiency between episodes (70). This form of diabetes is usually considered a form of type 2 diabetes (ketosis-prone type 2 diabetes), is strongly inherited, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected individuals may be intermittent. Future research is needed to determine the cause of β-cell dysfunction/destruction in this rare clinical scenario.

Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes are increasing (71). People with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and 25–50% are diagnosed with life-threatening DKA (30–32). Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes (47) or in children from the general population (72,73) can effectively identify those who will develop type 1 diabetes. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (42). These findings are highly significant, because while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both “sporadic” and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (55,74,75). In The Environmental Determinants of Diabetes in the Young (TEDDY) study, type 1 diabetes developed in 21% of 363 subjects with at least one autoantibody at 3 years of age (76). Such testing, coupled with education about diabetes symptoms and close follow-up, has been shown to enable earlier diagnosis and to prevent DKA (77,78).

Several screening programs are available in Europe (e.g., Fr1da and gppad.org) and the U.S. (e.g., trialnet.org, askhealth.org, and cascadekids.org). Family history of autoimmune diabetes and personal or family history of allergic diseases or other autoimmune diseases increases the risk of autoimmune diabetes compared with the general population (78,79). Individuals who test autoantibody positive should be provided with or referred for counseling about the risk of developing diabetes, diabetes symptoms, and DKA prevention and should be given consideration for additional testing as applicable to help determine if they meet criteria for intervention aimed at delaying progression.

PREDIABETES AND TYPE 2 DIABETES

Recommendations

2.9 Screening for prediabetes and type 2 diabetes with an assessment of risk factors or validated risk calculator should be done in asymptomatic adults. B

2.10a Testing for prediabetes or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors (**Table 2.4**). B

2.10b For all other people, screening should begin at age 35 years. B

2.11 If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (e.g., weight gain). C

2.12 To screen for prediabetes and type 2 diabetes, FPG, 2-h PG during 75-g OGTT, and A1C are each appropriate (**Table 2.1** and **Table 2.2**). B

2.13 When using OGTT as a screen for prediabetes or diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. A

2.14 Risk-based screening for prediabetes or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factors for diabetes. (See **Table 2.5** for evidence grading of risk factors.) B

2.15a Consider screening people for prediabetes or diabetes if on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV

Table 2.4—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors:
    - First-degree relative with diabetes
    - High-risk race and ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
    - History of cardiovascular disease
    - Hypertension (≥130/80 mmHg or on therapy for hypertension)
    - HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or a triglyceride level >250 mg/dL (>2.8 mmol/L)
    - Individuals with polycystic ovary syndrome
    - Physical inactivity
    - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (A1C ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV, exposure to high-risk medicines, history of pancreatitis

GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

medications, and second-generation antipsychotic medications, as these agents are known to increase the risk of these conditions. **E**

2.15b In people who are prescribed second-generation antipsychotic medications, screen for prediabetes and diabetes at baseline and repeat 12–16 weeks after medication initiation or sooner, if clinically indicated, and annually. **B**

2.16 People with HIV should be screened for diabetes and prediabetes with an FPG test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, FPG should be checked annually. **E**

Prediabetes

Prediabetes is the term used for individuals whose glucose or A1C levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism that results in elevated glucose levels (dysglycemia) intermediate between normoglycemia and diabetes (28,80). People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) (**Table 2.2**). As prediabetes is an intermediate state between normoglycemia and diabetes, it is clearly a significant risk factor for progression to diabetes as well as cardiovascular disease and several other cardiometabolic outcomes. Criteria for screening for diabetes or prediabetes in asymptomatic adults are outlined in **Table 2.4**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

Diagnosis of Prediabetes

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (78,79) and IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (10). It should be noted that the World Health Organization and a number of diabetes organizations define the IFG lower limit at 110 mg/dL (6.1 mmol/L). The ADA also initially endorsed this IFG lower limit in 1997 (10). However, in 2003 the ADA adopted the new range of 100–125 mg/dL (5.6–6.9 mmol/L) to better define IFG so that the population risk of developing diabetes with IFG would be similar to that with IGT (11).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as defined by A1C criteria demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5% and 6.0% (between 37 and 42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9% to 25%). Those with an A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25% and 50% and a relative risk 20 times higher than that with A1C of 5.0% (31 mmol/mol) (81). In a community-based study of African American and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (82). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (83), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (7).

Table 2.5—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- Race and ethnicity (e.g., Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **B**

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile is deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

An A1C range of 5.7–6.4% (39–47 mmol/mol) identifies a group of individuals at high risk for diabetes and cardiovascular outcomes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% (39–47 mmol/mol) should be informed of their increased risk for diabetes and cardiovascular disease and counseled about effective strategies to lower their risks (see Section 3, “Prevention or Delay of Diabetes and Associated Comorbidities”). Similar to glucose measurements, the continuum of risk is continuous: as A1C rises, the diabetes risk rises disproportionately (81). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C $>$6.0% [$>$42 mmol/mol] and individuals with both IFG and IGT).

Table 2.4 outlines the criteria for screening for prediabetes. The ADA risk test is an additional option for assessment to determine the appropriateness of screening for diabetes or prediabetes in asymptomatic adults (**Fig. 2.2**) (online at diabetes.org/socrisktest). For additional background regarding risk factors and screening for prediabetes, see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN ASYMPTOMATIC ADULTS and SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS, below. For details regarding individuals with prediabetes most likely to benefit from a formal behavioral or lifestyle intervention, see Section 3, “Prevention or Delay of Diabetes and Associated Comorbidities.”

Type 2 Diabetes

Type 2 diabetes accounts for 90–95% of all diabetes. This form encompasses individuals who generally have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance (i.e., decreased biological response to insulin).

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and individuals do not have any of the other known causes of diabetes. Most, but not all, people with type 2 diabetes have overweight or obesity. Excess weight itself causes some degree of insulin resistance. Individuals who do not have obesity or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region, including sites involved in nonalcoholic fatty liver disease (also known as metabolic dysfunction-associated steatotic liver disease) and/or ectopic sites (e.g., skeletal muscle).

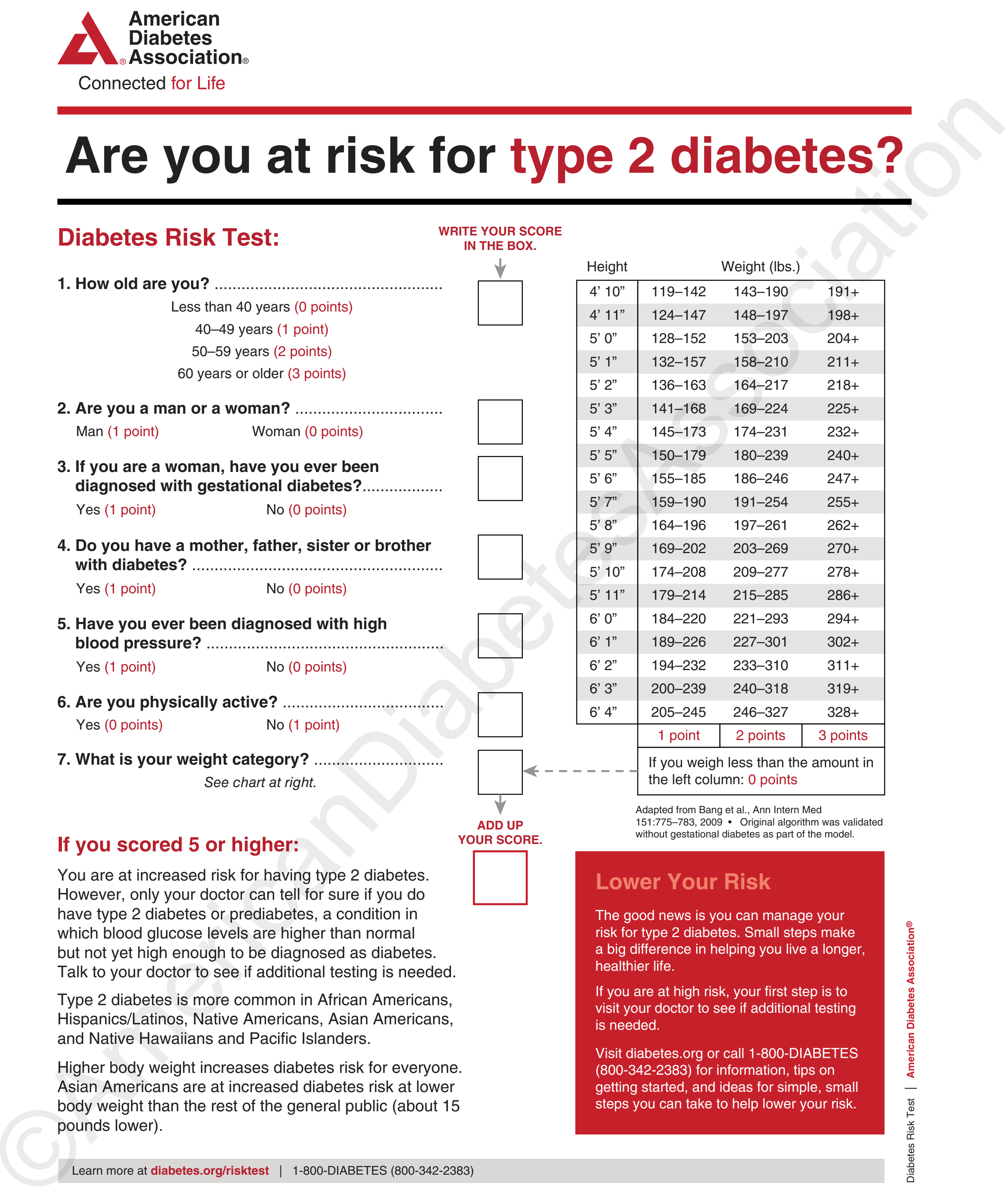
DKA seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in individuals already treated with insulin (e.g., missed or inadequate doses), in people with ketosis-prone type 2 diabetes, in association with the stress of another illness such as infection (e.g., COVID-19) or myocardial infarction, or in association with illicit drug use (e.g., cocaine) or with the use of certain medications such as glucocorticoids, second-generation antipsychotics, or sodium–glucose cotransporter 2 inhibitors (84,85). Type 2 diabetes frequently goes undiagnosed for many years, because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the individual to notice the classic diabetes symptoms caused by hyperglycemia, such as dehydration or unintentional weight loss. Nevertheless, even undiagnosed people with diabetes are at increased risk of developing macrovascular and microvascular complications.

People with type 2 diabetes early in the disease course may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion that is insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive diet and exercise, newer pharmacological agents (e.g., glucagon-like peptide 1 receptor agonists), or surgical weight loss have led to diabetes remission (86–92) (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”).

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity (93,94). It occurs more frequently in individuals with prediabetes, prior gestational diabetes mellitus, or polycystic ovary syndrome. It is also more common in people with hypertension or dyslipidemia and in certain racial and ethnic subgroups (e.g., African American, Native American, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes). However, the genetics of type 2 diabetes are poorly understood and under intense investigation in this era of precision medicine (52). In adults without traditional risk factors for type 2 diabetes and/or of younger age, consider islet autoantibody testing (e.g., GAD autoantibodies) to exclude the diagnosis of type 1 diabetes (36) (**Fig. 2.1**).

Screening and Testing for Prediabetes and Type 2 Diabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes risk through a targeted assessment of risk factors (**Table 2.4**) or with an assessment tool, such as the ADA risk test (**Fig. 2.2**) (online at diabetes.org/socrisktest), is recommended to guide health care professionals on whether performing a diagnostic test (**Table 2.1**) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection via screening is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available (95). The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes. It is important to individualize risk-to-benefit ratio of formal intervention for people with prediabetes and consider person-centered goals. Risk models have explored the benefit, in general finding higher benefit of intervention in those at highest risk (96) (see Section 3, “Prevention or Delay of Diabetes and Associated Comorbidities”) and reduce the risk of diabetes complications (97) (see Section 10, “Cardiovascular Disease and Risk Management,” Section 11, “Chronic Kidney Disease and Risk Management,” and Section 12, “Retinopathy, Neuropathy, and Foot Care”). In the most recent National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (98) resulted in lower rates of developing retinopathy and nephropathy (99). Similar impact on diabetes complications was reported with screening, diagnosis, and comprehensive risk factor management in the U.K. Clinical Practice Research Datalink database (97). In that report, progression from



American Diabetes Association®
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you? .... ☐

Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman? .... ☐

Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?................. ☐

Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? .... ☐

Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure? .... ☐

Yes (1 point) No (0 points)

6. Are you physically active? .... ☐

Yes (0 points) No (1 point)

7. What is your weight category? .... ☐

See chart at right.

ADD UP YOUR SCORE. ☐

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at **diabetes.org/risktest** | 1-800-DIABETES (800-342-2383)

Diabetes Risk Test | American Diabetes Association®

Figure 2.2—ADA risk test (diabetes.org/socrisktest).

prediabetes to diabetes augmented risk of complications.

Despite the numerous benefits of screening and early diagnosis for prediabetes or diabetes, unfortunately many people in the U.S. and globally either remain undiagnosed or are diagnosed late, when complications have already arisen.

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic individuals are described below.

Age

Age is a major risk factor for diabetes. Testing should begin at no later than age 35 years for all people (100). Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

Medications

Certain medications, such as glucocorticoids, statins (101), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, thiazide diuretics, some HIV medications (19), and second-generation antipsychotic medications (102), should be considered when deciding whether to screen for prediabetes or diabetes, as these medications are known to increase the risks of these conditions.

For example, people taking second-generation antipsychotic medications, such as olanzapine, require greater monitoring because of an increase in risk of type 2 diabetes associated with this medication (102). There is a range of effects on metabolic parameters (e.g., glucose concentration, hyperglycemia, and weight gain) across second-generation antipsychotic medications; aripiprazole and ziprasidone tend to have fewer metabolic effects, and haloperidol, clozapine, quetiapine, and risperidone tend to have more metabolic effects. People treated with these agents should be screened for prediabetes or diabetes at baseline, rescreened 12–16 weeks after medication initiation, and screened annually thereafter (102).

People With HIV

People with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies; a screening protocol is therefore recommended (103). The A1C test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring (20). In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among people with HIV and diabetes, preventive health care using an approach used in people without HIV is critical to reduce the risks of microvascular and macrovascular complications. Diabetes risk is increased with certain protease inhibitors (PIs) and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). New-onset diabetes is estimated to occur in more than 5% of individuals infected with HIV on PIs, whereas more than 15% may have prediabetes (104).

PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For people with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (105). Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, antihyperglycemic agents may still be necessary.

Testing Interval

The appropriate interval between screening tests is not known (106). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced, and individuals with false-negative tests will be retested before substantial time elapses and complications develop (106). In especially high-risk individuals, particularly with weight gain, shorter intervals between screenings may be useful.

Community Screening

Ideally, screening should be carried out within a health care setting because of the need for follow-up and treatment. Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (107).

Screening in Dental Practices

Because periodontal disease is associated with diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (108–110), with one study estimating that 30% of individuals ≥30 years of age seen in general dental practices (including people with and without periodontal disease) had newly diagnosed dysglycemia (110). A similar study in 1,150 dental patients >40 years old in India reported 20.7% and 14.6% meeting criteria for prediabetes and diabetes, respectively, using random blood glucose (111). Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

Screening and Testing for Prediabetes and Type 2 Diabetes in Children and Adolescents

The epidemiologic studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations (112). However, recent ADA clinical guidance concluded that A1C, FPG, or 2-h PG could be used to test for prediabetes or type 2 diabetes in children and adolescents (113).

In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in racial and ethnic minority populations (114). See **Table 2.5** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (113). See **Table 2.1** and **Table 2.2** for the criteria for the diagnosis of diabetes and prediabetes, respectively, that apply to children, adolescents, and adults. See Section 14, “Children and Adolescents,” for additional information on type 2 diabetes in children and adolescents.

PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS

Recommendation

2.17 Screen people for diabetes within 3–6 months following an episode of acute pancreatitis and annually thereafter. Screening for diabetes is recommended annually for people with chronic pancreatitis. **E**

Pancreatic diabetes (also termed pancreatogenic diabetes or type 3c diabetes) includes both structural and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. The diverse set of etiologies includes pancreatitis (acute and chronic), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed later in this section), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders, and idiopathic forms (2); as such, pancreatic diabetes is the preferred umbrella term (115).

Pancreatitis, even a single bout, can lead to postpancreatitis diabetes mellitus. Both acute and chronic pancreatitis can lead to postpancreatitis diabetes mellitus, and the risk is highest with recurrent bouts. A distinguishing feature is concurrent pancreatic exocrine insufficiency (consider screening individuals with acute and chronic pancreatitis for exocrine pancreatic insufficiency by measuring fecal elastase), pathological pancreatic imaging (endoscopic ultrasound, MRI, and computed tomography), and absence of type 1 diabetes–associated autoimmunity (116–120). There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications appears to be similar to that of other forms of diabetes.

For people with pancreatitis and diabetes, therapy should be advanced if A1C goals are not met. Glucose-lowering therapies associated with increased risk of pancreatitis (i.e., incretin-based therapies) should be avoided. Early initiation of insulin therapy should be considered. In the context of pancreatectomy, islet autotransplantation can be considered for selected individuals with medically refractory chronic pancreatitis in specialized centers to preserve endogenous islet function and insulin secretion (121,122). In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements (123).

Cystic Fibrosis–Related Diabetes

Recommendations

2.18 Annual screening for cystic fibrosis–related diabetes (CFRD) with an OGTT should begin by age 10 years in all people with cystic fibrosis not previously diagnosed with CFRD. **B**

2.19 A1C is not recommended as a screening test for CFRD due to low sensitivity. However, a value of ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD. **B**

2.20 Beginning 5 years after the diagnosis of CFRD, annual monitoring for complications of diabetes is recommended. **E**

Cystic fibrosis is a multisystem condition arising from recessive mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Pancreatic exocrine damage ultimately manifests as pancreatic exocrine insufficiency that begins as early as infancy (124). Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults (125). The relevance of CFRD is highlighted by its association with increased morbidity, mortality, and patient burden. Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β-cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. OGTT is the recommended screening test for CFRD. Not unexpectedly, annual OGTTs are perceived as burdensome, and adherence to current CFRD screening guidelines is poor, with only 30% of adults with cystic fibrosis having annual OGTTs (126). A1C is not recommended for screening due to low sensitivity; however, a value ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD and reduces patient screening burden (127–129). Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (127,128). The Cystic Fibrosis Foundation Patient Registry (130) evaluated 3,553 people with cystic fibrosis and diagnosed 445 (13%) with CFRD. Early diagnosis and treatment of CFRD was associated with preservation of lung function. The European Cystic Fibrosis Society Patient Registry reported an increase in CFRD with age (10% increase per decade), genotype, decreased lung function, and female sex (131,132). CGM or HOMA of β-cell function (133) may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking these results to long-term outcomes is lacking, and these tests are not recommended for screening outside the research setting (134).

CFRD mortality has significantly decreased over time, and the gap in mortality between people with cystic fibrosis with and without diabetes has considerably narrowed (135). There are limited clinical trial data on therapy for CFRD. People with CFRD should be treated with insulin to attain individualized glycemic goals.

Additional resources for the clinical management of CFRD can be found in the position statement “Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes” (136) and in the International Society for Pediatric and Adolescent Diabetes 2018 clinical practice consensus guidelines (125).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

2.21 After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of posttransplantation diabetes mellitus (PTDM) is best made once the individual is stable on an immunosuppressive plan and in the absence of an acute infection. **B**

2.22 The OGTT is the preferred test to make a diagnosis of PTDM. **B**

2.23 Immunosuppressive plans shown to provide the best outcomes for individuals and graft survival should be used, irrespective of PTDM risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (137). New-onset diabetes after transplantation (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes people with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (138). Another term, posttransplantation diabetes mellitus

(PTDM) (138,139), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset (140). The clinical importance of PTDM lies in its unquestionable impact as a significant risk factor for cardiovascular disease and chronic kidney disease in solid-organ transplantation (137).

Hyperglycemia is very common during the early posttransplant period, with ∼90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (138,139,141,142). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (142,143). Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM, and the role of the diabetes health care professional is to treat hyperglycemia appropriately regardless of the type of immunosuppression (138). Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, obesity, etc.) and transplant-specific factors, such as use of immunosuppressant agents (144–146). Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the individual is stable on maintenance immunosuppression (usually at least 45 days after transplantation) and in the absence of acute infection (138,142–144,147).

The OGTT is considered the gold-standard test for the diagnosis of PTDM (1 year posttransplant) (138,139,148,149). Pretransplant elevation in hs-CRP was associated with PTDM in the setting of renal transplant (150,151). However, screening people with FPG and/or A1C can identify high-risk individuals who require further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM (144,152,153). Most studies have reported that transplant patients with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (142,144,154). Insulin therapy is the agent of choice for the management of hyperglycemia, PTDM, preexisting diabetes, and diabetes in the hospital setting and can be continued postdischarge. No studies to date have firmly established which noninsulin agents are safest or most efficacious in PTDM. The choice of agent is usually made based on the side effect profile of the medication, possible interactions with the individual's immunosuppression plan, and potential cardiovascular and renal benefits in individuals with PTDM (144). Well-designed intervention trials examining the efficacy and safety of these and other antihyperglycemic agents in people with PTDM are needed.

MONOGENIC DIABETES SYNDROMES

Recommendations

2.24a Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**

2.24b Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and who often have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young (MODY). **A**

2.24c In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, are present in a small fraction of people with diabetes (<5%) (155). **Table 2.6** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see "Genetic Diagnosis of Endocrine Disorders" (156).

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed neonatal or congenital diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (36,157–160). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β-cell K_{ATP} channel. A recent report details a de novo mutation in *EIF2B1* affecting eIF2 signaling associated with permanent neonatal diabetes and hepatic dysfunction, similar to Wolcott-Rallison syndrome but with few severe comorbidities (161). The recent ADA-European Association for the Study of Diabetes type 1 diabetes consensus report recommends that regardless of current age, individuals diagnosed under 6 months of age should have genetic testing (36). Correct diagnosis has critical implications, because 30–50% of people with K_{ATP}-related neonatal diabetes will exhibit improved blood glucose levels when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, and while intensive insulin management is currently the preferred treatment strategy, there are important genetic counseling considerations, as most of the mutations that cause diabetes are dominantly inherited.

Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 13 genes on different chromosomes identified to date (162). The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

For individuals with MODY, the treatment implications are considerable and warrant genetic testing (163,164). Clinically, people with GCK-MODY exhibit mild, stable fasting hyperglycemia and do not require antihyperglycemic therapy, although it is commonly needed during pregnancy. Individuals with HNF1A-MODY or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy; in some instances, insulin will

Table 2.6—Most common causes of monogenic diabetes

	Gene	Inheritance	Clinical features
MODY	*HNF1A*	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [>5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	GCK	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [<3 mmol/L])
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1*, *HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (157)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

Adapted from Carmody et al. (156). AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

be required over time. Mutations or deletions in *HNF1B* are associated with renal cysts and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes, including *PDX1* (*IPF1*) and *NEUROD1*.

Diagnosis of Monogenic Diabetes

A diagnosis of one of the three most common forms of MODY, including HNF1A-MODY, GCK-MODY, and HNF4A-MODY, allows for more cost-effective personalized therapy (i.e., no therapy for GCK-MODY and sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members and can indicate potential extrapancreatic complications in affected individuals. Genetic screening (i.e., next-generation sequencing) is increasingly available and cost-effective (161,163).

A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes, although admittedly, atypical diabetes is becoming increasingly difficult to precisely define in the absence of a definitive set of tests for either type of diabetes (158–160,163–169) (**Fig. 2.1**). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in people with monogenic diabetes has been reported (170). Individuals in whom monogenic diabetes is suspected should be referred to a specialist for further evaluation. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (170), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. A biomarker screening pathway, such as the combination of urinary C-peptide/creatinine ratio and antibody screening, may aid in determining who should get genetic testing for MODY (171). It is critical to correctly diagnose one of the monogenic forms of diabetes, because these individuals may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment plans and delays in diagnosing other family members (172). The correct diagnosis is especially critical for those with GCK-MODY mutations, where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy (173). It has been reported that low hs-CRP can be used in identifying those more likely to have HNF1A-MODY as opposed to other forms of diabetes, supporting genetic testing in such individuals (174). The risks of microvascular and macrovascular complications with HNF1A-MODY and HNF4A-MODY are similar to those observed in people with type 1 and type 2 diabetes (175,176). Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis and to address comprehensive cardiovascular risk.

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations) (157,177)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, and lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.6–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

GESTATIONAL DIABETES MELLITUS

Recommendations

2.25 In individuals who are planning pregnancy, screen those with risk factors (**Table 2.4**) **B** and consider testing all individuals of childbearing potential for undiagnosed prediabetes or diabetes. **E**

2.26a Before 15 weeks of gestation, test individuals with risk factors (**Table 2.4**) **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.

2.26b Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus (GDM) diagnosis. **B** Early treatment for individuals with abnormal glucose metabolism may provide some benefit. **E**

2.26c Screen for early abnormal glucose metabolism with dysglycemia using FPG of 110–125 mg/dL (6.1–6.9 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). **B**

2.27 Screen for GDM at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. **A**

2.28 Screen individuals with GDM for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g OGTT and clinically appropriate nonpregnancy diagnostic criteria. **A**

2.29 Individuals with a history of GDM should have lifelong screening for the development of prediabetes or diabetes at least every 3 years. **B**

Definition

For many years, gestational diabetes mellitus (GDM) was defined as any degree of glucose intolerance that was first recognized during pregnancy (81), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has serious limitations (178). First, the best available evidence reveals that many cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant individuals of reproductive age. It is the severity of hyperglycemia that is clinically important regarding both short- and long-term maternal and fetal risks.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in people of reproductive age, with an increase in the number of pregnant individuals with undiagnosed type 2 diabetes in early pregnancy (179–181). Ideally, undiagnosed diabetes should be identified preconception in individuals with risk factors or in high-risk populations (182–187), as the preconception care of people with preexisting diabetes results in lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age birth weight, and neonatal intensive care unit admission (188). If individuals are not screened prior to pregnancy, universal early screening at <15 weeks of gestation for undiagnosed diabetes may be considered over selective screening (**Table 2.4**), particularly in populations with high prevalence of risk factors and undiagnosed diabetes in people of childbearing age. Strong racial and ethnic disparities exist in the prevalence of undiagnosed diabetes. Therefore, early screening provides an initial step to identify these health disparities so that they can begin to be addressed (184–187). Standard diagnostic criteria for identifying undiagnosed diabetes in early pregnancy are the same as those used in the nonpregnant population (**Table 2.1**). Individuals found to have diabetes by the standard diagnostic criteria used outside of pregnancy should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly.

Early abnormal glucose metabolism, defined as a fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9% (41 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, and perinatal death), are more likely to need insulin treatment, and are at high risk of a later GDM diagnosis (189–194). An A1C threshold of 5.7% has not been shown to be associated with adverse perinatal outcomes (195,196).

If early screening is negative, individuals should be rescreened for GDM between 24 and 28 weeks of gestation (see Section 15, “Management of Diabetes in Pregnancy”). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT, as well as the GDM screening and diagnostic criteria used in the two-step approach, were not derived from data in the first half of pregnancy and should not be used for early screening (197). To date, most randomized controlled trials of treatment of early abnormal glucose metabolism have been underpowered for outcomes. A recent randomized controlled trial performed at 17 centers administered early screening (mean 15.6 ± 2.5 weeks) for GDM with a 75-g OGTT. Individuals who met World Health Organization criteria for GDM were randomized to receive early treatment or a repeat OGTT at 24–28 weeks (with deferred treatment if indicated). The first primary outcome measure was an adverse neonatal composite outcome including birth <37 weeks, birth weight ≥4.5 kg, birth trauma, neonatal respiratory distress within 24 h of birth, phototherapy, stillbirth neonatal death, or shoulder dystocia. Early GDM treatment resulted in a significant but modest improvement in the composite adverse neonatal outcome (24.9% early treatment vs. 30.5% control, relative risk 0.82 [0.68–0.98]), with a suggestion of more benefit (per prespecified subgroup analyses) among individuals who had the OGTT at <14 weeks and among individuals with glycemic values in higher ranges on their OGTTs (198). Therefore, the benefits of treatment for early abnormal glucose metabolism remain uncertain. Nutrition counseling and periodic "block" testing of glucose levels weekly to identify individuals with high glucose levels are suggested. Testing frequency may proceed to daily, and treatment may be intensified, if the FPG is predominantly >110 mg/dL (>6.1 mmol/L) prior to 18 weeks of gestation.

Both the FPG and A1C are low-cost tests. An advantage of the A1C test is its convenience, as it can be added to the prenatal laboratories and does not require an early-morning fasting appointment. Disadvantages include inaccuracies in the presence of increased red blood cell turnover and hemoglobinopathies (usually reads lower) and higher values with anemia and reduced red blood cell turnover (199). A1C is not reliable for screening for GDM or for preexisting diabetes at 15 weeks of gestation or later; if the first screening takes place at this stage, one cannot differentiate between preexisting diabetes and GDM with an A1C.

GDM is often indicative of underlying β-cell dysfunction (200), which confers marked increased risk for later development of diabetes, generally but not always type 2 diabetes, in the mother after delivery (201,202). As effective prevention interventions are available (203,204), individuals diagnosed with GDM should receive lifelong screening for prediabetes to allow interventions to reduce diabetes risk and for type 2 diabetes to allow treatment at the earliest possible time (205).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (206), a large-scale multinational cohort study completed by more than 23,000 pregnant individuals, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM.

GDM diagnosis (**Table 2.7**) can be accomplished with either of two strategies:

1. The "one-step" 75-g OGTT derived from the IADPSG criteria, or
2. The older "two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive based on the work of Carpenter-Coustan's interpretation of the older O'Sullivan and Mahan (207) criteria.

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading some experts to debate, and disagree on, optimal strategies for the diagnosis of GDM.

One-Step Strategy

The IADPSG defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in individuals at 24–28 weeks of gestation who participated in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis (208). Many regional studies have investigated the impact of adopting the IADPSG criteria on prevalence and have seen a roughly one- to threefold increase (209). The anticipated increase in the incidence of GDM could have a substantial impact on costs and medical infrastructure needs and has the potential to "medicalize" pregnancies previously categorized as normal. A follow-up study of individuals participating in a study of pregnancy OGTTs with glucose levels blinded to caregivers found that 11 years after their pregnancies, individuals who would have been diagnosed with GDM by the one-step approach, as compared with those without GDM, were at 3.4-fold higher risk of developing prediabetes and type 2 diabetes and had children with a higher risk of obesity and increased body fat, suggesting that the larger group of individuals identified as having GDM by the one-step approach would benefit from the increased screening for diabetes and prediabetes after pregnancy (210). The ADA recommends the IADPSG diagnostic criteria with the intent of optimizing gestational outcomes, because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

The expected benefits of using IADPSG criteria to the offspring are inferred from intervention trials that focused on individuals with lower levels of hyperglycemia than those identified using older GDM diagnostic criteria. Those trials found modest benefits, including reduced rates of large-for-gestational-age births and preeclampsia (211,212). It is important to note that 80–90% of participants being treated for mild GDM in these two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped the thresholds recommended by the IADPSG, and in one trial (212), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]).

No randomized controlled trials of treating versus not treating GDM diagnosed by the IADPSG criteria but not the Carpenter-Coustan criteria have been published to date. However, a recent randomized trial of testing for GDM at 24–28 weeks of gestation by the one-step method using IADPSG criteria versus the two-step method using a 1-h 50-g glucose loading test (GLT) and, if positive, a 3-h OGTT by Carpenter-Coustan criteria identified twice as many individuals with GDM using the one-step method compared with the two-step method. Despite treating more individuals for GDM using the one-step method, there was no difference in pregnancy and perinatal complications (213). However, concerns have been raised about sample size estimates and unanticipated suboptimal engagement with the protocol regarding screening and treatment. For example, in the two-step group, 165 participants who did not get counted as having GDM were treated for isolated elevated FPG >95 mg/dL (>5.3 mmol/L) (214). The high prevalence of prediabetes in people of childbearing age may support the more inclusive IADPSG criteria. National Health and Nutrition Examination Survey (NHANES) data demonstrate a 21.5% prevalence of prediabetes in people of reproductive age of 20–44 years, which is comparable to or higher than the prevalence of GDM diagnosed by the one-step method (215).

The one-step method identifies the long-term risks of maternal prediabetes and diabetes and offspring abnormal glucose metabolism and adiposity. Post hoc GDM in individuals diagnosed by the

Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when an individual is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively),* proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the individual is fasting.

The diagnosis of GDM is made when at least two† of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [226]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. *American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (222). †ACOG notes that one elevated value can be used for diagnosis (222).

one-step method in the HAPO cohort was associated with higher prevalence of IGT; higher 30-min, 1-h, and 2-h glucoses during the OGTT; and reduced insulin sensitivity and oral disposition index in their offspring at 10–14 years of age compared with offspring of mothers without GDM. Associations of mother's fasting, 1-h, and 2-h values on the 75-g OGTT were continuous with a comprehensive panel of offspring metabolic outcomes (216, 217). In addition, HAPO Follow-up Study (HAPO FUS) data demonstrate that neonatal adiposity and fetal hyperinsulinemia (cord C-peptide), both higher across the continuum of maternal hyperglycemia, are mediators of childhood body fat (218).

Data are lacking on how the treatment of mother's hyperglycemia in pregnancy affects her offspring's risk for obesity, diabetes, and other metabolic disorders (219,220). Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of individuals with GDM diagnosed by the one-step strategy.

Two-Step Strategy

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (221). The 15-member panel had representatives from obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended a two-step approach to screening that used a 1-h 50-g GLT followed by a 3-h 100-g OGTT for those who screened positive. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (222). Updated from 2014, a 2021 U.S. Preventive Services Task Force systematic review continued to conclude that one-step versus two-step screening is associated with increased likelihood of GDM (11.5% vs. 4.9%) but without improved health outcomes. It reported that the oral glucose challenge test using thresholds of 140 or 135 mg/dL had sensitivities of 82% and 93% and specificities of 82% and 79%, respectively, against Carpenter-Coustan criteria. FPG cutoffs of 85 mg/dL and 90 mg/dL had sensitivities of 88% and 81% and specificities of 73% and 82%, respectively, against Carpenter-Coustan criteria (223). The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (224).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of individuals with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and therefore is easier to accomplish for many individuals. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (225), and shoulder dystocia without increasing small-for-gestational-age births. ACOG currently supports the two-step approach but notes that one elevated value, as opposed to two, may be used for the diagnosis of GDM (222). If this approach is implemented, the incidence of GDM by the two-step strategy will likely increase markedly. ACOG recommends either of two sets of diagnostic thresholds for the 3-h 100-g OGTT Carpenter-Coustan or National Diabetes Data Group (226,227). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan and Mahan (207), which used whole blood and nonenzymatic methods for glucose determination. A secondary analysis of data from a randomized clinical trial of identification and treatment of mild GDM (228) demonstrated that treatment was similarly beneficial in people meeting only the lower thresholds per Carpenter-Coustan (226) and in those meeting only the higher thresholds per National Diabetes Data Group (227). If the two-step approach is used, it would appear advantageous to use the Carpenter-Coustan lower diagnostic thresholds, as shown in step 2 in **Table 2.7**.

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. A systematic review of economic evaluations of GDM screening found that the one-step method identified more cases of GDM and was more likely to be cost-effective than the two-step method (229). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

The IADPSG criteria (one-step strategy) have been adopted internationally as the preferred approach. Data that compare population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (213,230–232). In addition, pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have outcomes comparable to pregnancies with diagnosed GDM by the more stringent two-step criteria (233,234). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit people with GDM, caregivers, and policymakers. Longer-term outcome studies are currently underway.

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3. Prevention or Delay of Diabetes and Associated Comorbidities: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For guidelines related to screening for increased risk for type 2 diabetes (prediabetes), please refer to Section 2, "Diagnosis and Classification and of Diabetes." For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 14, "Children and Adolescents."

Recommendations

3.1 In people with prediabetes, monitor for the development of type 2 diabetes at least annually; modify based on individual risk assessment. **E**

3.2 In people with preclinical type 1 diabetes, monitor for disease progression using A1C approximately every 6 months and 75-g oral glucose tolerance test (i.e., fasting and 2-h plasma glucose) annually; modify frequency of monitoring based on individual risk assessment based on age, number and type of autoantibodies, and glycemic metrics. **E**

Screening for prediabetes and type 2 diabetes risk through an assessment of risk factors (**Table 2.5**) or with an assessment tool, such as the American Diabetes Association risk test (**Fig. 2.2**), is recommended to guide whether to perform a diagnostic test for prediabetes (**Table 2.2**) and type 2 diabetes (**Table 2.1**) (see Section 2, "Diagnosis and Classification of Diabetes"). Testing high-risk adults for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost, substantial time exists before the development of type 2 diabetes and its complications during which one can intervene, and there are effective approaches delaying type 2 diabetes in those with prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance (IGT), or impaired fasting glucose (IFG). The utility of screening with A1C for prediabetes

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A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.

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and diabetes may be limited in the presence of hemoglobinopathies and conditions that affect red blood cell turnover. See Section 2, “Diagnosis and Classification of Diabetes,” and Section 6, “Glycemic Goals and Hypoglycemia,” for additional details on the appropriate use and limitations of A1C testing.

Three distinct stages of type 1 diabetes have been defined, with symptomatic type 1 diabetes being stage 3 (**Table 2.3**). In individuals at risk for development of clinical type 1 diabetes, younger age of seroconversion (particularly under age 3 years), the total number of diabetes related autoantibodies (1), and the development of autoantibodies against islet antigen 2 (IA-2) have all been associated with more rapid progression to clinical type 1 diabetes. While continuous glucose monitoring can predict progression to overt diabetes in children with autoantibodies (2), oral glucose tolerance testing–based metrics are superior in predicting progression compared with continuous glucose monitoring (3). The decision to perform an oral glucose tolerance test may depend on such factors as eligibility and interest for stage-specific treatments, participation in clinical research, and availability and burden of testing.

LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION

Recommendations

3.3 Refer adults with overweight or obesity at high risk of type 2 diabetes, as seen in the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity. **A**

3.4 A variety of eating patterns can be considered to prevent type 2 diabetes in individuals with prediabetes. **B**

3.5 Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed. **E**

3.6 Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial (4), the Finnish Diabetes Prevention Study (DPS) (5), and the Da Qing Diabetes Prevention Study (Da Qing study) (6), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation) (7). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (4). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large trials of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study (8), 43% reduction at 7 years in the Finnish DPS (5), and 34% reduction at 10 years (9) and 27% reduction at 15 years (10) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals (11). The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min of moderate-intensity physical activity per week, such as brisk walking. Although weight loss was the most important factor in reducing the risk of incident diabetes, achieving the behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% (12).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes (as well as improve other cardiometabolic risk factors). Participants were encouraged to achieve the ≥7% weight loss during the first 6 months of the intervention. Further analysis suggests higher benefit for prevention of diabetes with at least 7–10% weight loss with lifestyle interventions (12). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant’s initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the dietary intervention was on reducing total fat rather than calories. After several weeks, the concept of calorie balance and the need to restrict calories and fat was introduced (11).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (11).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population (11).

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors (such as how to choose healthy food options when eating out), and guidance on managing psychological, social, and motivational challenges. Further details are available regarding the core curriculum sessions (11).

Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total dietary fat and calories (4,11,12). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (13). Based on other trials, a variety of eating patterns (13,14) may also be appropriate for individuals with prediabetes (13), including Mediterranean-style and low-carbohydrate eating plans (15–18). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (19–22). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (21,23–25). As is the case for those with diabetes, individualized medical nutrition therapy (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (26).

Physical Activity

Moderate-intensity physical activity, such as brisk walking for 150 min/week, has shown beneficial effects in those with prediabetes (4). Similarly, moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (27,28). Health care professionals are encouraged to promote a DPP-style program to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training (11,29,30). Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels (31,32). The effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM) (33).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payers ensued (34–38). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (39–43).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (cdc.gov/diabetes/prevention/index.htm). This online resource includes locations of CDC-recognized diabetes prevention lifestyle change programs (cdc.gov/diabetes/prevention/find-a-program.html). To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test (cdc.gov/prediabetes/takethetest/). During the first 4 years of implementation of the CDC’s National DPP, 36% achieved the 5% weight loss goal (44). The CDC has also developed the Diabetes Prevention Impact Tool Kit (nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP (45). To expand preventive services using a cost-effective model, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP to organizations recognized by the CDC that become Medicare suppliers for this service (innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, individuals must have BMI $>$25 kg/m^2 (or BMI $>$23 kg/m^2 if self-identified as Asian) and glycemic testing consistent with prediabetes in the last year. Medicaid coverage of the National DPP is also expanding on a state-by-state basis.

While CDC-recognized behavioral counseling programs, including Medicare DPP services, have met minimum quality standards and are reimbursed by many payers, lower retention rates have been reported for younger adults and racial and ethnic minority populations (46). Therefore, other programs and modalities of behavioral counseling for diabetes prevention may also be appropriate and efficacious based on individual preferences and availability. The use of community health workers to support DPP-like interventions has been shown to be effective and cost-effective (47,48) (see Section 1, “Improving Care and Promoting Health in Populations,” for more information). The use of community health workers may facilitate the adoption of behavior changes for diabetes prevention while bridging barriers related to social determinants of health. However, coverage by third-party payers remains limited. Counseling by a registered dietitian nutritionist (RDN) has been shown to help individuals with prediabetes improve eating habits, increase physical activity, and achieve 7–10% weight loss (13,49–51). Individualized medical nutrition therapy (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (26,49). Furthermore, trials involving medical nutrition therapy for adults with prediabetes found significant reductions in weight, waist circumference, and glycemia. Individuals with prediabetes can benefit from referral to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment plan (50,52). Other health care professionals, such as pharmacists and diabetes care and education specialists, may be considered for diabetes prevention efforts (53,54).

Technology-assisted programs may effectively deliver a DPP-like intervention (55–60). A digital diabetes prevention program improved cardiovascular risk at 4 months but not at 12 months (61). Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for individuals with low income and people in rural locations; however, not all technology-assisted programs are effective (55,62–64). The CDC Diabetes Prevention Recognition Program (DPRP) (cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based interventions; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Health care professionals should consider referring adults with prediabetes to certified technology-assisted programs.

Lifestyle and Type 1 Diabetes Progression

Observational studies suggest that in those with islet autoantibodies, factors that may increase β-cell demand including less physical activity (65), higher dietary glycemic index (66), and total sugar intake (67) are associated with progression to clinical diabetes. Similar associations have not been seen in the development of autoantibodies. In The Environmental Determinants of Diabetes in the Young (TEDDY) longitudinal study, daily minutes spent in moderate to vigorous physical activity were associated with a reduced risk of progression to type 1 diabetes in children 5 to 15 years of age with multiple islet autoantibodies (hazard ratio [HR] 0.92 [95% CI 0.86–0.99] per 10-min increase; $P = 0.021$) (65). In the Diabetes Autoimmunity Study in the Young (DAISY), in children with islet autoantibodies, progression to type 1 diabetes was associated with higher dietary glycemic index (HR 2.20 [95% CI 1.17–4.15]) and total sugar intake (HR 1.75 [95% CI 1.07–2.85]) (66,67). In nonobese diabetic mice, an animal model for the development of type 1 diabetes, sustained high glucose drinking significantly aggravated islet inflammation and accelerated the onset of type 1 diabetes (68). Lifestyle interventions focusing on such factors in those with stage 1 or stage 2 type 1 diabetes have not yet been reported.

PHARMACOLOGIC INTERVENTIONS

Recommendations

3.7 Metformin for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL [≥6 mmol/L]), and higher A1C (e.g., ≥6.0% [≥42 mmol/mol]), and in individuals with prior gestational diabetes mellitus. **A**

3.8 Long-term use of metformin may be associated with vitamin B12 deficiency; consider periodic assessment of vitamin B12 level in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in diet and physical activity can be difficult to maintain long term (9), people at high risk of type 2 diabetes may benefit from additional support and pharmacotherapeutic options, if needed. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, incretin receptor agonists (e.g., liraglutide and semaglutide), thiazolidinediones, and insulin have been shown to lower the incidence of diabetes in specific populations (69–74), whereas diabetes prevention was not seen with nateglinide (75).

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years (12). In individuals with previous history of GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline (76). Several medications evaluated for weight loss (e.g., orlistat, phentermine/topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of type 2 diabetes in those with prediabetes (74,77–79).

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan or testosterone (80,81), but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs (81–84). Although the Vitamin D and Type 2 Diabetes (D2d) prospective randomized controlled trial showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (85), post hoc analyses and meta-analyses suggest a potential benefit in specific populations (85–89). Further research is needed to define characteristics and clinical indicators where vitamin D supplementation may be of benefit (80).

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for prevention of type 2 diabetes. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost and burden of administration.

Metformin has the most safety data as a pharmacologic therapy for diabetes prevention (90). Metformin was overall less effective than lifestyle modification in the DPP, though group differences attenuated over time in the DPPOS (10), and metformin may be cost-saving over a 10-year period (36). In the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥35 kg/m^2 and in younger participants aged 25–44 years (4). In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (91). Both interventions remained highly effective during a 10-year follow-up period (92). By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose (≥110 mg/dL [≥6 mmol/L] vs. 95–109 mg/dL [5.3–5.9 mmol/L]), those with a higher A1C (6.0–6.4% [42–46 mmol/mol] vs. <6.0% [<42 mmol/mol]), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that may benefit the most from metformin (93). In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; however, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (94). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., younger individuals, those with history of GDM, or those with BMI ≥35 kg/m^2). A recent Chinese open-label randomized controlled trial showed that metformin combined with standard lifestyle intervention further reduced the risk of developing diabetes than lifestyle intervention alone by ∼17% over 2 years (95). Periodic assessment of vitamin B12 level in those taking metformin chronically should be considered to check for possible deficiency, especially in those with anemia or peripheral neuropathy (96,97) (see Section 9, "Pharmacologic Approaches to

Glycemic Treatment," for more details). The effect of metformin on vitamin B12 increases with time (98), with a higher risk for vitamin B12 deficiency ($<$150 pmol/L) noted at 4–5 years. A person who has been on metformin for more than 4 years or is at risk for vitamin B12 deficiency for other reasons (e.g., vegan, previous gastric/small bowel surgery) should be monitored for vitamin B12 deficiency annually (99).

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Recommendations

3.9 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

3.10 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued for this adverse effect. **B**

3.11 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fractures. **A** Lower doses may mitigate the risk of adverse effects but may be less effective. **C**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (100), and are at increased risk for cardiovascular disease (101,102). Evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (103–105), and individuals should be monitored for diabetes development and receive evidence-based lifestyle behavior change for diabetes prevention described in this section. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (106,107). The lifestyle intervention in the Da Qing study was associated with lowering cardiovascular disease and mortality at 23 and 30 years of observational follow-up (6,8). Treatment goals and therapies for hypertension and dyslipidemia in the primary and secondary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular diseases risk factors (108). Statin use increases risk of diabetes (109–113). In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled HR [95% CI] for incident diabetes 1.36 [1.17–1.58]) (111). In trials of primary and secondary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes (114,115), suggesting a favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins is not recommended in this population due to concerns of diabetes risk.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk (see Section 10, "Cardiovascular Disease and Risk Management," for more details). The IRIS (Insulin Resistance Intervention after Stroke) trial of people with a recent ($<$6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance (as defined by a HOMA of insulin resistance index of $\geq$3.0), evaluated pioglitazone (target dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower in the pioglitazone group than with placebo; weight gain, edema, and fractures were higher in the pioglitazone treatment group (116–119). Lower doses may mitigate the adverse effects but may also be less effective (120).

PERSON-CENTERED CARE GOALS

Recommendations

3.12 In adults with overweight or obesity at high risk of type 2 diabetes, care goals should include weight loss and maintenance, minimizing the progression of hyperglycemia, and attention to cardiovascular risk. **B**

3.13 Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, and cardiovascular risk reduction) may be considered to support person-centered care goals. **B**

3.14 More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI $\geq$35 kg/m^2, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6.1–6.9 mmol/L], 2-h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], and A1C $\geq$6.0% [$\geq$42 mmol/mol]), and individuals with a history of gestational diabetes mellitus. **A**

Individualized risk-to-benefit ratio should be considered in screening, intervention, and monitoring to lower the risk of type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications (121,122). Prediabetes is associated with increased cardiovascular disease and mortality (102), which emphasizes the importance of attending to cardiovascular risk in this population.

In the DPP, which enrolled high-risk individuals with IGT, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo group was 11 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 29% (4). Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases per 100 person-years) included BMI $\geq$35 kg/m^2, higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6–6.9 mmol/L], 2-h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], and A1C $\geq$6.0% [$\geq$42 mmol/mol]), and a history of GDM (4,91,92). In contrast, in the community-based Atherosclerosis Risk in Communities (ARIC) study, observational follow-up of adults with mean age 75 years with laboratory evidence of prediabetes (based on A1C 5.7–6.4% [39–47 mmol/mol] and/or fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L]), but not meeting specific BMI criteria, found lower progression to diabetes over 6 years: 9% of those with A1C-defined prediabetes, 8% with IFG (122).

Thus, it is important to individualize the risk-to-benefit ratio of intervention and consider person-centered goals. Risk models have generally found higher benefit of the intervention in those at highest risk (12). Diabetes prevention trials and observational studies highlight key principles that may guide person-centered goals. In the DPP, which enrolled a high-risk population meeting criteria for overweight or obesity, weight loss was an important mediator of diabetes prevention or delay, with greater metabolic benefit seen with greater weight loss (12,123). In the DPP/DPPOS, progression to diabetes, duration of diabetes, and mean level of glycemia were important determinants of the development of microvascular complications (10). Achieving normal glucose regulation, even once, during the DPP was associated with a lower risk of diabetes and lower risk of microvascular complications (124). Observational follow-up of the Da Qing study also showed that regression from IGT to normal glucose tolerance or remaining with IGT rather than progressing to type 2 diabetes at the end of the 6-year intervention trial resulted in significantly lower risk of cardiovascular disease and microvascular disease over 30 years (125).

Pharmacotherapy for weight management (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes,” for more details), minimizing the progression of hyperglycemia (see Section 9, “Pharmacologic Approaches to Glycemic Treatment,” for more details), and cardiovascular risk reduction (see Section 10, “Cardiovascular Disease and Risk Management,” for more details) can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

PHARMACOLOGIC INTERVENTIONS TO DELAY SYMPTOMATIC TYPE 1 DIABETES

Recommendation

3.15 Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes (stage 3) should be considered in selected individuals aged ≥8 years with stage 2 type 1 diabetes. Management should be in a specialized setting with appropriately trained personnel. **B**

Teplizumab has been approved to delay the onset of stage 3 type 1 diabetes in people 8 years of age and older with stage 2 type 1 diabetes based in part on the results of a single trial in relatives of people with type 1 diabetes (126). In this study, 44 individuals were randomized to a 14-day course of teplizumab and 32 to placebo. The median time to stage 3 type 1 diabetes diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group. Type 1 diabetes was diagnosed in 19 (43%) of participants who received teplizumab and 23 (72%) of those who received placebo (HR 0.41 [95% CI 0.22–0.78]). In prespecified analyses, the presence of HLA-DR4, absence of HLA-DR3, and absence of anti–zinc transporter 8 antibody predicted response to teplizumab (HR 0.20 [95% CI 0.09–0.45], 0.18 [0.07–0.45], and [0.07 [0.02 to 0.26], respectively). The most common adverse reactions were transient lymphopenia (73%) followed by rash (36%).

Numerous clinical studies are being conducted to test methods for preventing or delaying the onset of stage 3 type 1 diabetes in those with evidence of autoimmunity without symptoms or for delaying loss of insulin secretory capacity after onset of stage 3, some with promising results (see ClinicalTrials.gov and TrialNet.org).

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4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PERSON-CENTERED COLLABORATIVE CARE

Recommendations

4.1 A person-centered communication style that uses person-centered, culturally sensitive, and strength-based language and active listening; elicits individual preferences and beliefs; and assesses literacy, numeracy, and potential barriers to care should be used to optimize health outcomes and health-related quality of life. **B**

4.2 People with diabetes can benefit from a coordinated interprofessional team that may include and is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and behavioral health professionals. **E**

A successful medical evaluation depends on beneficial interactions between the person with diabetes and the care team. The Chronic Care Model (1–3) (see Section 1, "Improving Care and Promoting Health in Populations") is a person-centered approach to care that requires a close working relationship between the person with diabetes and clinicians involved in treatment planning. People with diabetes should receive health care from a coordinated interprofessional team that may include but is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, behavioral health professionals, and community partners such as community health workers and community paramedics. Individuals with diabetes and their care partners must assume an active role in their care. Based on the preferences

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**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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The BONE HEALTH subsection has received endorsement from the American Society for Bone and Mineral Research.

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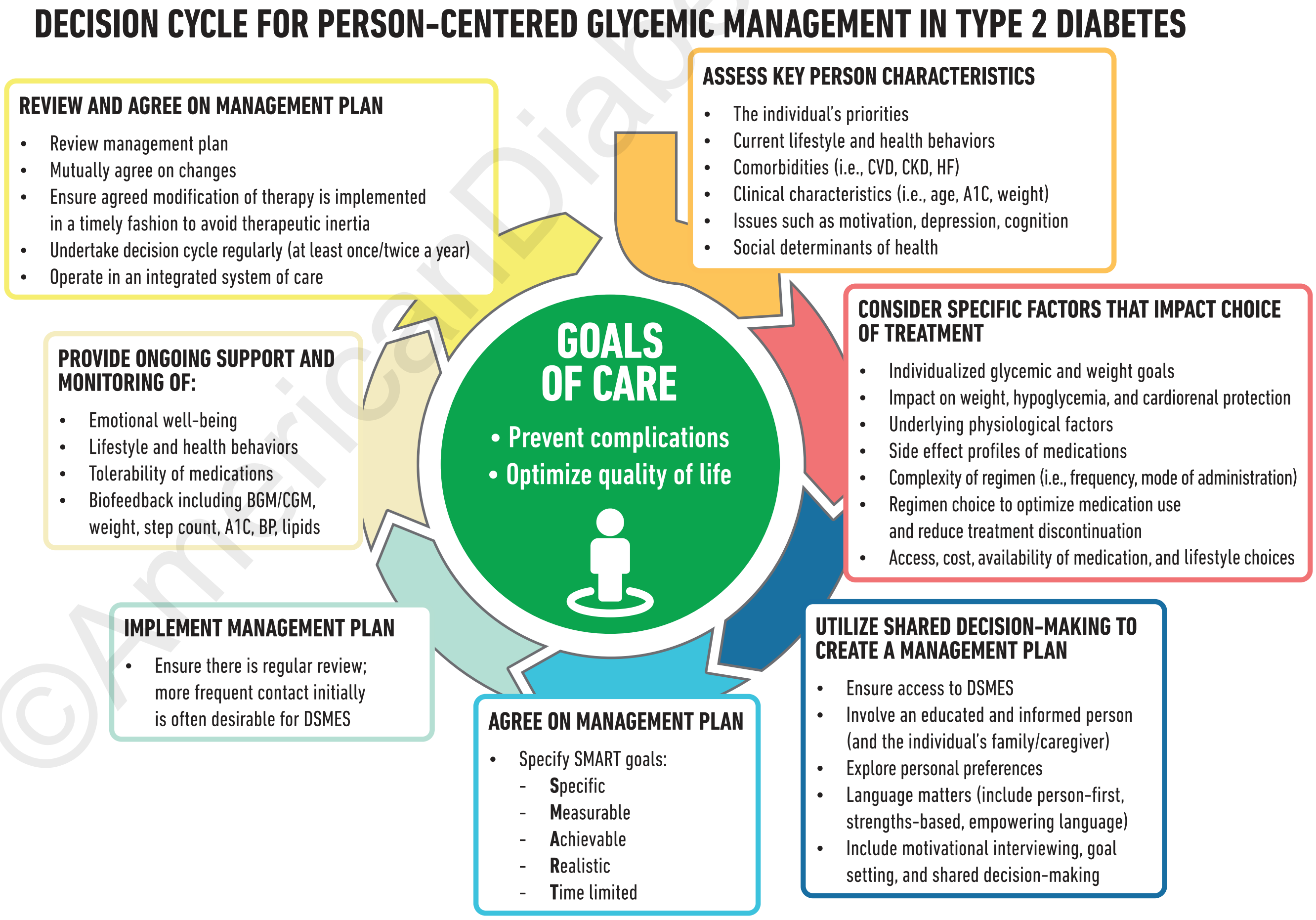
and values of the person with diabetes, elicited by the care team, the family or support group and health care team together formulate the management plan, which includes lifestyle management (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes").

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life (**Fig. 4.1**). Treatment goals and plans should be cocreated with people with diabetes based on their individual preferences, values, and goals. This individualized management plan should take into account the person's age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy), diabetes history (duration, complications, and current use of medications), comorbidities, disabilities, health priorities, other medical conditions, preferences for care, access to health care services, and life expectancy. People living with diabetes should be engaged in conversation about these aspects of their lives and diabetes management, with routine reassessment as necessary given their changing circumstances across the life span. Various strategies and techniques should be used to support the person's self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management.

Health care professional communication with people with diabetes and families should acknowledge that multiple factors impact glycemic management but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (4–8). Thus, the goal of communication between health care professionals and people with diabetes is to establish a collaborative relationship and to assess and address self-management barriers without blaming people with diabetes for "noncompliance" or "nonadherence" when the outcomes of self-management are not optimal (9). The familiar terms noncompliance and nonadherence denote a passive, obedient role for a person with diabetes in "following doctor's orders" that is at odds with the active role people with diabetes take in directing the day-to-day decision-making, planning, monitoring, evaluation, and problem-solving involved in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in management and the role systemic factors play may help minimize the person's resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the person said, can help facilitate communication. Perceptions of people with diabetes about their own ability, or self-efficacy, to self-manage diabetes constitute one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes (10–12) and should be goals of ongoing assessment, education, and treatment planning.


DECISION CYCLE FOR PERSON-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES
GOALS OF CARE
• Prevent complications
• Optimize quality of life

ASSESS KEY PERSON CHARACTERISTICS
- The individual's priorities
- Current lifestyle and health behaviors
- Comorbidities (i.e., CVD, CKD, HF)
- Clinical characteristics (i.e., age, A1C, weight)
- Issues such as motivation, depression, cognition
- Social determinants of health

CONSIDER SPECIFIC FACTORS THAT IMPACT CHOICE OF TREATMENT
- Individualized glycemic and weight goals
- Impact on weight, hypoglycemia, and cardiorenal protection
- Underlying physiological factors
- Side effect profiles of medications
- Complexity of regimen (i.e., frequency, mode of administration)
- Regimen choice to optimize medication use and reduce treatment discontinuation
- Access, cost, availability of medication, and lifestyle choices

UTILIZE SHARED DECISION-MAKING TO CREATE A MANAGEMENT PLAN
- Ensure access to DSMES
- Involve an educated and informed person (and the individual's family/caregiver)
- Explore personal preferences
- Language matters (include person-first, strengths-based, empowering language)
- Include motivational interviewing, goal setting, and shared decision-making

AGREE ON MANAGEMENT PLAN
- Specify SMART goals:
  - **S**pecific
  - **M**easurable
  - **A**chievable
  - **R**ealistic
  - **T**ime limited

IMPLEMENT MANAGEMENT PLAN
- Ensure there is regular review; more frequent contact initially is often desirable for DSMES

PROVIDE ONGOING SUPPORT AND MONITORING OF:
- Emotional well-being
- Lifestyle and health behaviors
- Tolerability of medications
- Biofeedback including BGM/CGM, weight, step count, A1C, BP, lipids

REVIEW AND AGREE ON MANAGEMENT PLAN
- Review management plan
- Mutually agree on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid therapeutic inertia
- Undertake decision cycle regularly (at least once/twice a year)
- Operate in an integrated system of care

Figure 4.1—Decision cycle for person-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (294). BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, atherosclerotic cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure.

Language has a strong impact on perceptions and behavior. Empowering language can help to inform and motivate, while shame and judgement can be discouraging. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (formerly called the American Association of Diabetes Educators) joint consensus report, "The Use of Language in Diabetes Care and Education," provides the authors' expert opinion regarding the use of language by health care professionals when speaking or writing about diabetes for people with diabetes or for professional audiences (13). Although further research is needed to address the impact of language on diabetes outcomes, the report includes five key consensus recommendations for language use:

- Use language that is neutral, nonjudgmental, and based on facts, actions, or physiology/biology.
- Use language free from stigma.
- Use language that is strength based, respectful, and inclusive and that imparts hope.
- Use language that fosters collaboration between people with diabetes and health care professionals.
- Use language that is person centered (e.g., "person with diabetes" is preferred over "diabetic").

COMPREHENSIVE MEDICAL EVALUATION

Recommendations

4.3 A complete medical evaluation should be performed at the initial visit to:

- Confirm the diagnosis and classify diabetes. **A**
- Evaluate for diabetes complications, potential comorbid conditions, and overall health status. **A**
- Identify care partners and support system. **E**
- Assess social determinants of health and structural barriers to optimal health and health care. **A**
- Review previous treatment and risk factor management in people with established diabetes. **A**
- Begin engagement with the person with diabetes in the formulation of a care management plan including initial goals of care. **A**
- Develop a plan for continuing care. **A**

4.4 A follow-up visit should include most components of the initial comprehensive medical evaluation (**Table 4.1**). **A**

4.5 Ongoing management should be guided by the assessment of overall health status, diabetes complications, cardiovascular risk, hypoglycemia risk, and shared decision-making to set therapeutic goals. **B**

The comprehensive medical evaluation includes the initial and follow-up evaluations, assessment of complications, psychosocial assessment, management of comorbid conditions, overall health, functional and cognitive status, and engagement of the person with diabetes throughout the process. While a comprehensive list is provided in **Table 4.1**, in clinical practice the health care professional may need to prioritize the components of the medical evaluation given the available resources and time. Engaging other members of the health care team can also support comprehensive diabetes care. The goal of these recommendations is to provide the health care team information so it can optimally support people with diabetes and their care partners. In addition to the medical history, physical examination, and laboratory tests, health care professionals should assess diabetes self-management behaviors, nutrition, social determinants of health, and psychosocial health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") and give guidance on routine immunizations. The assessment of sleep pattern and duration should be considered. Interval follow-up visits should occur at least every 3–6 months individualized to the person and then at least annually.

Lifestyle management and behavioral health care are cornerstones of diabetes management. People with diabetes should be referred for diabetes self-management education and support, medical nutrition therapy, and assessment of behavioral health concerns as appropriate. People with diabetes should receive recommended preventive care services (e.g., immunizations and cancer screening); smoking cessation counseling; and ophthalmological, dental, podiatric, and other referrals, as needed.

The assessment of risk of acute and chronic diabetes complications and treatment planning are key components of initial and follow-up visits (**Table 4.2**). The risk of atherosclerotic cardiovascular disease and heart failure (see Section 10, "Cardiovascular Disease and Risk Management"), chronic kidney disease staging (see Section 11, "Chronic Kidney Disease and Risk Management"), presence of retinopathy and presence of neuropathy (see Section 12, "Retinopathy, Neuropathy, and Foot Care"), and risk of treatment-associated hypoglycemia should be used to individualize goals for glycemia (see Section 6, "Glycemic Goals and Hypoglycemia"), blood pressure, and lipids and to select specific glucose-lowering medication(s) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"), antihypertension medication(s), and statin treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.3**). Clinicians should ensure that people with diabetes are appropriately screened for complications, comorbidities, and treatment burden. Discussing and implementing an approach to glycemic management with the person is a part, not the sole goal, of the clinical encounter.

IMMUNIZATIONS

Recommendation

4.6 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.4**). **A**

Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (14,15). The Centers for Disease Control and Prevention (CDC) provides vaccination schedules specifically for children, adolescents, and adults with diabetes (cdc.gov/vaccines/). The CDC Advisory Committee on Immunization Practices (ACIP) makes recommendations based on its own review and rating of the evidence, provided in **Table 4.4** for selected vaccinations. The ACIP evidence review has evolved over time with the adoption of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) in 2010 and then the Evidence to Decision or Evidence to Recommendation frameworks in 2020 (16). Here, we discuss the particular importance of specific vaccines.

COVID-19

People with underlying medical conditions, including diabetes, are more likely

Table 4.1 - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment plans and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Common comorbidities (e.g., obesity, OSA, NAFLD)	✓		
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Macrovascular and microvascular complications	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam			✓
	▪ Visits to specialists			✓
	▪ Disability assessment and use of assistive devices (e.g., physical, cognitive, vision and auditory, history of fractures, podiatry)	✓	✓	✓
	▪ Personal history of autoimmune disease	✓		
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓
BEHAVIORAL FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Assess familiarity with carbohydrate counting (e.g., type 1 diabetes, type 2 diabetes treated with MDI)	✓		✓
	▪ Physical activity and sleep behaviors; screen for obstructive sleep apnea	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication plan	✓	✓	✓
	▪ Medication-taking behavior, including rationing of medications and/or medical equipment	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use, connected pen and glucose data	✓	✓	✓
SOCIAL LIFE ASSESSMENT	**Social network**			
	▪ Identify existing social supports	✓		✓
	▪ Identify surrogate decision maker, advanced care plan	✓		✓
	▪ Identify social determinants of health (e.g., food security, housing stability & homelessness, transportation access, financial security, community safety)	✓		✓
	▪ Assess daily routine and environment, including school/work schedules and ability to engage in diabetes self-management	✓	✓	✓

Continued on p. S5

Table 4.1 (cont.) - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination	✓		✓
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓	✓	✓
	• Screen for PAD (pedal pulses—refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, diabetes distress, fear of hypoglycemia, and disordered eating	✓		✓
	▪ Consider assessment for cognitive performance*	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
	▪ Consider assessment for bone pain	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in people with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin	✓		✓
	• Complete blood count (CBC) with platelets	✓		✓
	• Serum potassium levels in people with diabetes on ACE inhibitors, ARBs, or diuretics+	✓		✓
	• Calcium, vitamin D, and phosphorous for appropriate people with diabetes	✓		✓

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; CGM, continuous glucose monitors; MDI, multiple daily injections; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; PAD, peripheral arterial disease.

*At 65 years of age or older.

+May be needed more frequently in people with diabetes with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see **Table 11.1**).

#May also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications).

^In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent.

**Should be performed at every visit in people with diabetes with sensory loss, previous foot ulcers, or amputations.

to become severely ill with coronavirus disease 2019 (COVID-19) (see DIABETES AND COVID-19 section below). COVID-19 vaccinations and boosters are recommended for everyone ages 6 months and older in the U.S. for the prevention of COVID-19 (17).

Hepatitis B

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis. Because of the higher likelihood of transmission, hepatitis B vaccine is recommended for adults with diabetes aged $<$60 years. For adults aged $\geq$60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the person's likelihood of acquiring hepatitis B infection (18).

Influenza

Influenza is a common, preventable infectious disease associated with high mortality

Table 4.2—Assessment and treatment plan

Assessing risk of diabetes complications
- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (see Section 6, “Glycemic Goals and Hypoglycemia”)
- Assessment for retinopathy
- Assessment for neuropathy
- Assessment for NAFLD/NASH

Goal setting
- Set A1C/blood glucose/time in range
- If hypertension is present, establish blood pressure goal
- Weight management and physical activity goals
- Diabetes self-management goals

Therapeutic treatment plans
- Lifestyle management
- Pharmacologic therapy: glucose lowering
- Pharmacologic therapy: cardiovascular and kidney disease risk factors
- Weight management with pharmacotherapy or metabolic surgery, as appropriate
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education, behavioral health, and medical specialists

Assessment and treatment planning are essential components of initial and all follow-up visits. ASCVD, atherosclerotic cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

and morbidity in vulnerable populations, including youth, older adults, and people with chronic diseases. Influenza vaccination in people with diabetes has been found to significantly reduce influenza and diabetes-related hospital admissions (19). In people with diabetes and cardiovascular disease, influenza vaccine has been associated with lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (20). Given the benefits of the annual influenza vaccination, it is recommended for all individuals ≥6 months of age who do not have a contraindication. The live attenuated influenza vaccine, which is delivered by nasal spray, is an option for people who are 2–49 years of age and who are not pregnant, but people with chronic conditions such as diabetes are cautioned against taking the live attenuated influenza vaccine and are instead recommended to receive the inactive or recombinant influenza vaccination. For individuals ≥65 years of age, there may be additional benefit from the high-dose quadrivalent inactivated influenza vaccine (21).

Pneumococcal Pneumonia

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes are at increased risk for pneumococcal infection and have been reported to have a high risk of hospitalization and death, with a mortality rate as high as 50% (22). There are two types of vaccines available in the U.S., pneumococcal conjugate vaccines (PCV13, PCV15, and PCV20) and pneumococcal polysaccharide vaccine (PPSV23), with distinct schedules for children and adults.

It is recommended that all children receive a four-dose series of PCV13 or PCV15 by 15 months of age. For children with diabetes who have incomplete series by ages 2–5 years, the CDC recommends a catch-up schedule to ensure that these children have four doses. Children with diabetes between 6 and 18 years of age are also advised to receive one dose of PPSV23, preferably after receipt of PCV13.

Adults aged ≥65 years whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. If PCV15 is used, it should be followed by PPSV23.

Adults aged 19–64 years with certain underlying risk factors or other medical conditions whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. As for adults aged ≥65 years, if PCV15 is used, it should be followed by PPSV23.

The recommended interval between PCV15 and PPSV23 is ≥1 year. If PPSV23 is the only dose received, PCV15 or PCV20 may be given ≥1 year later.

For adults with immunocompromising conditions, cochlear implant, or cerebrospinal fluid leak, a minimum interval of 8 weeks can be considered for dosing of PCV15 and PPSV23 when PCV15 has been used.

Adults who received PCV13 should follow the previously recommended PPSV23 series (23–26). Adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a cause of respiratory illness in older adults. People with chronic conditions such as diabetes have a higher risk of severe illness. The Food and Drug Administration (FDA) approved the first vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged ≥60 years. On 21 June 2023, ACIP voted to recommend that adults aged ≥60 years may receive a single dose of an RSV vaccine, using shared clinical decision-making. The ACIP Respiratory Syncytial Virus Vaccines Adult Work Group continues to monitor the efficacy

Table 4.3—Referrals for initial care management

- Eye care professional for annual dilated eye exam
- Family planning for individuals of childbearing potential
- Registered dietitian nutritionist for medical nutrition therapy
- Diabetes self-management education and support
- Dentist for comprehensive dental and periodontal examination
- Behavioral health professional, if indicated
- Audiology, if indicated
- Social worker/community resources, if indicated
- Rehabilitation medicine or another relevant health care professional for physical and cognitive disability evaluation, if indicated
- Other appropriate health care professionals

Table 4.4—Highly recommended immunizations for adults with diabetes (Advisory Committee on Immunization Practices and Centers for Disease Control and Prevention)

Vaccine	Recommended ages	Schedule	GRADE evidence type*	References
COVID-19	Recommended for all 6 months of age and older	Current initial vaccination and boosters		Centers for Disease Control and Prevention, Interim Clinical Considerations for Use of COVID-19 Vaccines, 2023 (295)
Hepatitis B	Recommended for adults with diabetes aged <60 years; for adults aged ≥60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the person's likelihood of acquiring hepatitis B infection			Weng et al., Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (18)
Influenza	All people with diabetes advised not to receive live attenuated influenza vaccine	Annual		Centers for Disease Control and Prevention, Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2023–24 Influenza Season (296)
Pneumonia (PPSV23 [Pneumovax])	19–64 years of age, vaccinate with Pneumovax	One dose is recommended for those who previously received PCV13; if PCV15 was used, follow with PPSV23 ≥1 year later; PPSV23 is not indicated after PCV20; adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose	2	Centers for Disease Control and Prevention, Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) (23)
	≥65 years of age	One dose is recommended for those who previously received PCV13; if PCV15 was used, follow with PPSV23 ≥1 year later; PPSV23 is not indicated after PCV20; adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose	2	Falkenhorst et al., Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) Against Pneumococcal Disease in the Elderly: Systematic Review and Meta-analysis (24)
PCV20 or PCV15	Adults 19–64 years of age, with an immunocompromising condition (e.g., chronic renal failure), cochlear implant, or cerebrospinal fluid leak	One dose of PCV15 or PCV20 is recommended by the Centers for Disease Control and Prevention	3	Kobayashi et al., Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (25)
	19–64 years of age, immunocompetent	For those who have never received any pneumococcal vaccine, the CDC recommends one dose of PCV15 or PCV20		
	≥65 years of age, immunocompetent, have shared decision-making discussion with health care professionals	One dose of PCV15 or PCV20; PCSV23 may be given ≥8 weeks after PCV15; PPSV23 is not indicated after PCV20		
RSV	Older adults ≥60 years of age with diabetes appear to be a risk group	Adults aged ≥60 years may receive a single dose of an RSV vaccine		Centers for Disease Control and Prevention, CDC Recommends RSV Vaccine for Older Adults (29)
Tetanus, diphtheria, pertussis (Tdap)	All adults; pregnant individuals should have an extra dose	Booster every 10 years	2 for effectiveness, 3 for safety	Havers et al., Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2019 (297)

Continued on p. S59

Table 4.4—Continued

Vaccine	Recommended ages	Schedule	GRADE evidence type*	References
Zoster	≥50 years of age	Two-dose Shingrix, even if previously vaccinated	1	Dooling et al., Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines (298)

For a comprehensive list of vaccines, refer to the Centers for Disease Control and Prevention web site at cdc.gov/vaccines/. Advisory Committee on Immunization Practices recommendations can be found at cdc.gov/vaccines/acip/recommendations. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV 20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. *Evidence type: 1, randomized controlled trials (RCTs) or overwhelming evidence from observational studies; 2, RCTs with important limitations or exceptionally strong evidence from observational studies; 3, observational studies or RCTs with notable limitations; 4, clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

of these vaccines among adults aged ≥60 years (27–29).

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and people with diabetes need to be aware of common comorbidities that affect people with diabetes and that may complicate management (30–32). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. This section discusses many of the common comorbidities observed in people with diabetes but is not necessarily inclusive of all the conditions that have been reported.

Autoimmune Diseases

Recommendations

4.7 People with type 1 diabetes should be screened for autoimmune thyroid disease soon after diagnosis and periodically thereafter. **B**

4.8 Adults with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease. **B**

People with type 1 diabetes are at increased risk for other autoimmune diseases, with thyroid disease, celiac disease, and pernicious anemia (vitamin B12 deficiency) being among the most common (33). Other associated conditions include autoimmune liver disease, primary adrenal insufficiency (Addison disease), collagen vascular diseases, and myasthenia gravis (34–37). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (38). Given the high prevalence, nonspecific symptoms, and insidious onset of primary hypothyroidism, routine screening for thyroid dysfunction is recommended for all people with type 1 diabetes. Screening for celiac disease should be considered in adults with diabetes with suggestive symptoms (e.g., diarrhea, malabsorption, and abdominal pain) or signs (e.g., osteoporosis, vitamin deficiencies, and iron deficiency anemia) (39,40). Measurement of vitamin B12 levels should be considered for people with type 1 diabetes and peripheral neuropathy or unexplained anemia.

Table 4.5—General and diabetes-specific risk factors for fracture

General risk factors
- Prior osteoporotic fracture
- Age >65 years
- Low BMI
- Sex
- Malabsorption
- Recurrent falls
- Glucocorticoid use
- Family history
- Alcohol/tobacco abuse
- Rheumatoid arthritis

Diabetes-specific risk factors
- Lumbar spine or hip T-score ≤−2.0
- Frequent hypoglycemic events
- Diabetes duration >10 years
- Diabetes medications: insulin, thiazolidinediones, sulfonylurea
- A1C >8%
- Peripheral and autonomic neuropathy
- Retinopathy and nephropathy

Bone Health

Recommendations

4.9 Fracture risk should be assessed in older adults with diabetes as a part of routine care in diabetes clinical practice, according to risk factors and comorbidities. **A**

4.10 Monitor bone mineral density using dual-energy X-ray absorptiometry of high-risk older adults with diabetes (aged >65 years) and younger individuals with diabetes and multiple risk factors every 2–3 years. **A**

4.11 Clinicians should consider the potential adverse impact on bone health when selecting pharmacological options to lower glucose levels in people with diabetes. Prioritizing medications with a proven safety profile for bones is recommended, particularly for those at elevated risk for fractures. **A**

4.12 To reduce the risk of falls and fractures, glycemic management goals should be individualized for people with diabetes at a higher risk of fracture. **C** Prioritize use of glucose-lowering medications that are associated with low risk for hypoglycemia to avoid falls. **E**

4.13 Advise people with diabetes on their intake of calcium and vitamin D to ensure it meets the recommended daily allowance for those at risk for fracture, either through their diet or supplemental means. **B**

4.14 Antiresorptive medications and osteoanabolic agents should be considered for people with diabetes who have low bone mineral density with a T-score ≤ -2.0 or have experienced fragility fractures. **B**

Fracture risk has traditionally relied on measurements of bone mineral density (BMD) and the World Health Organization–defined T-score of ≤ -2.5 SD. However, it is now established that the consideration of other risk factors improves the categorization of fracture risk (**Table 4.5**). There are factors beyond BMD testing that contribute to bone strength in people with diabetes.

Hip or vertebral fracture with low trauma in people aged ≥65 years is diagnostic for osteoporosis independent of BMD and is one of the strongest risk factors for subsequent fractures, especially in the first 1–2 years after a fracture (41,42). Osteoporotic hip fractures are associated with significant morbidity, mortality, and societal costs (43). It is estimated that 20% of individuals do not survive to 1 year after hip fracture, while 60% do not regain their prior functionality, living with permanent disability (44).

Hip fractures in people with diabetes are associated with higher risk of mortality (28% in women and 57% in men), longer recovery, and delayed healing (45) compared with individuals without diabetes.

Epidemiology and Risk Factors

Age-specific fracture risk is significantly increased in people with type 1 or type 2 diabetes in both sexes, with a 34% increase in fracture risk compared with those without diabetes (46).

Type 1 Diabetes. Fracture risk in people with type 1 diabetes is increased by 4.35 times for hip fractures, 1.83 times for upper limb fractures, and 1.97 times for ankle fractures (47). Fractures occur even at young ages, 10–15 years earlier than they do in people without diabetes, and are less frequent at the vertebral level. Type 1 diabetes is often associated with low bone mass, although BMD underestimates the high risk of fracture observed even in young individuals (47).

Type 2 Diabetes. In people with type 2 diabetes, hip fracture risk is increased by 1.79 times, and risk throughout life is 40–70% higher than in it is in individuals without diabetes (46,48). Fracture risk is increased also in the upper limbs and ankle. Hip fracture risk is increased even at early stages of the disease despite normal or higher BMD (49,50). However, bone loss is accelerated, and low BMD remains an independent risk factor for fractures (51).

Glucose control significantly impacts fracture risk in people with diabetes. A meta-analysis revealed an 8% increased fracture risk per 1% rise in A1C level (risk ratio [RR] 1.08 [95% CI 1.03–1.14]) (52). Poor glycemic control (A1C >9%) over 2 years in individuals with type 2 diabetes correlated with a 29% heightened fracture risk (53). Notably, this risk was higher in the White demographic than in other racial groups. Hypoglycemia also escalated the risk of fractures at the hip and other skeletal sites (RR 1.52 [95% CI 1.23–1.88]) (52). A Japanese study echoed these findings, showing a fracture risk increase (hazard ratio [HR] 2.24 [95% CI 1.56–3.21]) with severe hypoglycemia episodes (54).

Longer disease duration further elevates fracture risk (55); data indicate individuals with T2D for >10 years and those with type 1 diabetes for >26 years face significantly higher fracture risks, which are largely attributed to ensuing microvascular and macrovascular damage affecting the skeleton. Additionally, high fracture risk is seen in people with cardiovascular issues, nephropathy, retinopathy, neuropathy, and frequent falls (45, 56–59).

Certain glucose-lowering medications also factor into fracture risk. Studies have reported increased fracture incidences in women using thiazolidinediones (TZD), with the risk doubling with 1–2 years of TZD use (HR 2.23 [95% CI 1.65–3.01]) (60,61). According to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, reduced risk is noted in women who had discontinued TZD use for 1–2 years (HR 0.57 [95% CI 0.35–0.92]) or >2 years (HR 0.42 [95% CI 0.24–0.74]) compared with current users (62). Furthermore, individuals with type 2 diabetes on insulin (RR 1.49 [95% CI 1.29–1.73]) or sulfonylurea (RR 1.30 [95% CI 1.18–1.43]) treatment exhibit a heightened fracture risk (63).

Screening

Most evidence on screening in individuals at risk for fracture is available from people with type 2 diabetes, while fracture risk prediction in type 1 diabetes has not been explored. Health care professionals should assess fracture history and risk factors in older people with diabetes and recommend measurement of BMD if appropriate according to the individual's age and sex.

Type 2 Diabetes. People with type 2 diabetes have 5–10% higher BMD than people without diabetes. A T-score adjustment of −0.5 has been proposed to improve fracture prediction by dual-energy X-ray absorptiometry (DXA). For example, a T-score ≤ -2.0 should be interpreted as equivalent to −2.5 in a person without diabetes (51). Notably, the Fracture Risk Assessment Tool (FRAX), although useful, does not factor in type 2 diabetes; an inclusion of the condition is estimated to mirror the effect of either a 10-year age increase or a 0.5 SD reduction in BMD T-score (64). Fracture risk was higher in large observational studies in participants with diabetes compared with those without diabetes for a given T-score and age or for a given FRAX score (51). Additionally, integrating the diagnosis of rheumatoid arthritis in FRAX can potentially improve fracture risk prediction for people with type 2 diabetes. Growing evidence suggests that fracture risk prediction is enhanced by use of trabecular bone score (64), although such studies are not available for individuals with type 1 diabetes and are based on data from the U.S. or Canada.

In people with type 2 diabetes, in the absence of other comorbidities, DXA scan should be performed at least 5 years after the diagnosis of diabetes, and reassessment is recommended every 2–3 years (64) depending on the screening evaluation and the presence of additional risk factors (**Table 4.5**). According to the European Association for the Study of Obesity (EASO), DXA should be performed every two years in subjects undergoing bariatric-metabolic surgery.

Bone turnover markers are commonly used in clinical practice, although they are suppressed in people with diabetes and have not been shown to predict fracture risk (65).

Type 1 Diabetes. Because hip fracture risk in type 1 diabetes starts to increase after the age of 50, clinicians may consider assessing BMD after the 5th decade of life (47). In people with type 1 diabetes, BMD underestimates fracture risk, but studies do not address the extent of underestimation of fracture risk.

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), regular assessment of bone health using bone densitometry in youth with type 1 diabetes is still controversial and not recommended, but it may be considered in association with celiac disease because of the involvement of inflammatory pathways (66).

Management

Maintaining glucose control and minimizing hypoglycemic episodes are crucial for bone health in people with diabetes. Individuals with prolonged disease, microvascular and macrovascular complications, or frequent hypoglycemic episodes face higher fracture risks and fall risks due to factors like sarcopenia and impaired gait. Health care professionals should advocate moderate physical activity to enhance muscle health, gait coordination, and balance as part of fracture preventive strategies (58,59,67).

Aerobic and weight-bearing exercise should be recommended to counteract the potential negative effect of weight loss on bone; specific guidelines have been published for older adults with type 2 diabetes (68).

Osteoporosis and fracture prevention are first based on measures applied to the general population. All people with diabetes should receive an adequate daily intake of proteins, calcium, and vitamin D, stop smoking, and have regular physical activity (69–71).

Intake of calcium should reflect the age-specific recommendations of the general population and should be obtained through diet and/or oral supplements (72).

The optimal level of 25-hydroxyvitamin D is a matter of controversy (73), although serum levels $\geq$20 ng/mL are generally thought to be sufficient (74). Because diabetes is a risk factor for fractures, other guidelines suggest a goal $>$30 ng/mL (75).

The safe upper limit is also a matter of debate, and there is substantial disagreement over whether to treat to a specified serum level. In the U.S., the recommended daily allowance of vitamin D is 600 IU for people aged 51–70 years and 800 IU for people aged $>$70 years (74). In clinical practice, this dose of supplement is often not enough to reach recommended goals, and higher doses of D2 or D3 may be needed.

Fractures are main determinants of frailty, a predisability condition that should be mitigated with individualized interventions to prevent falls, maintain mobility, and delay disability (68). In many circumstances, conservative management (calcium, vitamin D, and lifestyle measures) are not enough to reduce fracture risk. When pharmacological treatment is needed, medication decision-making strategies are the same as those used for the general population. Antiosteoporosis medications reduce bone resorption (bisphosphonates, selective estrogen receptor modulators, and denosumab), stimulate bone formation (teriparatide and abaloparatide), or have dual actions by stimulating bone formation and reducing bone resorption (romosozumab). These agents improve bone density and reduce the risk of vertebral and nonvertebral fractures. Although there are no studies specifically designed for people with diabetes, data on antiresorptives and osteoanabolic agents suggest similar efficacy in type 2 diabetes compared with individuals without diabetes (76–78). Using individual patient data from randomized trials, antiresorptive therapies show similar effects in people with and without type 2 diabetes for vertebral, hip, and nonvertebral fractures (76). No similar studies of efficacy of antiosteoporosis treatment in people with type 1 diabetes have been published.

Primary Prevention of Fragility Fractures in People With Diabetes. In the general population, a T-score ≤ -2.5 is the threshold to consider pharmacological treatment for osteoporosis. In type 2 diabetes, since T-score underestimates fracture risk (as discussed above), a T-score ≤ -2.0 may be more appropriate for considering initiation of a first-line drug, including bisphosphonates (alendronate, risedronate, and zoledronate) or denosumab.

Denosumab is preferred in individuals with estimated glomerular filtration rate $<$30–35 mL/min/1.73 m^2. Self-management abilities of the person with diabetes should be considered in medication selection, as there can be rebound bone loss with missed doses of denosumab or delays in care. Zoledronic acid may be more appropriate in these cases.

Secondary Prevention of Fragility Fractures. The risk of subsequent fracture in individuals with hip or vertebral fracture is significantly high, especially in the first 1–2 years after a fracture. Antiosteoporosis treatment reduces the risk of fracture in older individuals with prior hip or vertebral fracture.

As in the general population, people with diabetes who experience fragility fracture should *1*) be given the diagnosis of osteoporosis regardless of DXA data and *2*) receive therapy to prevent future fractures (79). Individuals at particularly high risk (or those with multiple comorbidities) should be referred to a bone metabolic specialist. In these cases, a specialist may choose to initiate an osteoanabolic agent to optimize bone formation and reduce immediate fracture risk (80). It is strongly recommended that all individuals with a fragility fracture be started on antiosteoporosis therapy and adequate calcium and vitamin D supplementation, if needed, as early as possible, even during hospitalization (79).

There are some additional considerations related to medication selection in people with diabetes. Data from a phase 3 trial and population studies have indicated positive effects of denosumab on fasting glucose and on diabetes prevention. The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial and its 10-year extension have shown that people with diabetes treated with denosumab experience significant improvements in BMD and lower vertebral fracture risk but higher risk of nonvertebral fractures (81). Romosozumab, a newer anabolic medication, may be associated with increased risk of myocardial infarction and stroke, limiting its use in people with diabetes at higher risk for cardiovascular compilations (82,83).

Glucose-Lowering Medications and Bone Health

Care plans for type 2 diabetes treatment should consider individual fracture risk and the potential effect of medications on bone metabolism. Medications other than TZD are advisable for postmenopausal women or elderly men with type 2 diabetes due to their safer bone health profiles. While several studies have shown metformin has a safe profile, special attention should be paid to the wide use of sulfonylureas because of the high risk of hypoglycemic events and fractures (84). Dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have been used in clinical practice for more than 15 years, and both clinical trials and postmarketing data suggest a neutral impact on bone health (85,86). Tirzepatide may play a positive effect through glucose-dependent insulinotropic polypeptide (GIP) receptor agonism, preventing bone loss associated with weight loss (87).

Use of sodium–glucose cotransporter 2 inhibitors has raised some concerns. The Canagliflozin Cardiovascular Assessment Study (CANVAS) study showed that subjects treated with canagliflozin had a significant increase in fracture risk compared with placebo (HR 1.55). Further analyses from the same trial and from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study found a neutral effect on fracture risk (88–91). Although few data are available, use of empagliflozin, ertugliflozin, or dapagliflozin has not been associated with negative effects on bone health (90–92) Use of insulin has been shown to double the risk of hip fractures (84), likely because of higher risk of hypoglycemia, longer duration of the disease, and comorbidities.

In conclusion, glucose-lowering medications with good bone safety profiles should be preferred, especially in the elderly, in people with longer duration of disease, or in people with complications. Aggressive therapeutic approaches should be avoided in the frail and in the elderly to prevent hypoglycemic events and falls.

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (93). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (94), such as underlying disease physiology or diabetes treatments, although evidence for these links is scarce. People with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings, coordinated with their primary health care professional, and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking). New onset of atypical diabetes (lean body habitus and negative family history) in a middle-aged or older person may precede the diagnosis of pancreatic adenocarcinoma (95). However, in the absence of other symptoms (e.g., weight loss and abdominal pain), routine screening of all such individuals is not currently recommended. Metformin and sulfonylureas may have anticancer properties. Pioglitazone has mixed data, with a previous concern for bladder cancer association. Recommendations cannot be made at this time (96–98).

Cognitive Impairment/Dementia

Recommendation

4.15 In the presence of cognitive impairment, diabetes treatment plans should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (99,100). A meta-analysis of prospective observational studies found that individuals with diabetes had a 43% higher risk of all types of dementia, a 43% higher risk of Alzheimer dementia, and a 91% higher risk of vascular dementia compared with individuals without diabetes (101). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer dementia, and vascular dementia compared with rates in those with normal glucose tolerance (102). See Section 13, “Older Adults,” for a more detailed discussion regarding assessment of cognitive impairment.

Diabetes and COVID-19

Recommendations

4.16 Health care professionals should help people with diabetes aim to achieve individualized glycemic goals to reduce the risk of macrovascular and microvascular risk as well as reduce the risk of coronavirus disease 2019 (COVID-19) and its complications. **B**

4.17 As we move into the recovery phase, diabetes health care services and practitioners should address the impact of the COVID-19 pandemic in higher-risk groups, including minority, socioeconomically deprived, and older populations. **B**

4.18 People with diabetes who have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be followed up in the longer term to assess complications and symptoms of long COVID-19. **E**

4.19 New-onset diabetes cases should receive routine clinic follow-up to determine if the condition is transient. **B**

4.20 There is no clear indication to change prescribing of glucose-lowering therapies in people with diabetes infected by SARS-CoV-2. **B**

4.21 People with diabetes should be prioritized and offered SARS-CoV-2 vaccines and vaccine boosters. **B**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the clinical disease COVID-19, was first reported in December 2019 in China and has disproportionately impacted certain groups, including men, older people, racial and ethnic minority populations, and people with certain chronic conditions, including diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases. COVID-19 is now recognized as a complex multisystem disease with sequelae including widespread insulin resistance, endothelial dysfunction, hematological disorders, and hyperimmune responses (103). There is now evidence of not only direct but also indirect adverse effects of COVID-19 in people with diabetes. Many people with multiple long-term conditions have diabetes, which has also been associated with worse outcomes in people with COVID-19 (104). The association with BMI and COVID-19 mortality is U-shaped in both type 1 and type 2 diabetes (105).

COVID-19 has disproportionately affected certain groups, such as older people and those from some ethnic populations who are known to have high prevalence of chronic conditions such as diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases (106). In people with diabetes, higher blood glucose levels both prior to and during COVID-19 admission have been associated with poor outcomes, including mortality (107). Type 1 diabetes has been associated with higher risk of COVID-19 mortality than type 2 diabetes (108). The largest study of people with diabetes to date, using whole-population data from England with over 3 million people, reported a higher association for mortality in people with type 1 diabetes than type 2 diabetes (105). Male sex, older age, renal impairment, non-Hispanic White race, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19–related mortality in both type 1 and type 2 diabetes (105).

Much of the evidence for recommendations is from a recent systematic review that was commissioned by the World Health Organization on the latest research evidence on the impact of COVID-19 on people with diabetes (108). The review reported that there are no appropriate data to determine whether diabetes is a risk factor for acquiring SARS-CoV-2 infection. Diabetes is a risk factor for severe disease and death from COVID-19.

Reasons for the higher rates of COVID-19 and severity in minority ethnic groups are complex and could be due to higher prevalence of comorbid conditions (e.g., diabetes), differences in exposure risk (e.g., overcrowded living conditions and essential worker jobs), and access to treatment (e.g., health insurance status, specialist services, and medications), which all relate to long-standing structural inequities that vary by ethnicity (109).

There is now overwhelming evidence that approximately 30–40% of people who are infected with COVID-19 get persistent and sometimes relapsing and remitting symptoms 4 weeks after infection, which has been termed postacute sequelae of COVID-19, post-COVID-19 condition, postacute COVID-19 syndrome, or long COVID (110,111). Currently, data on long COVID specifically in people with diabetes are lacking, and people who have been infected with SARS-CoV-2 should be followed up in the longer term.

There have also been recent reports of development of new-onset diabetes in people who have had COVID-19. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known but may include previously undiagnosed diabetes presenting early or later in the disease trajectory, stress hyperglycemia, steroid-induced hyperglycemia, and possibly direct or indirect effects of SARS-CoV-2 on the β-cell (112). One large U.S. retrospective study of over 27 million people reported that COVID-19 was associated with significantly increased risk of new-onset type 1 diabetes and a disproportionately higher risk in ethnic minority populations (113). Another cross-sectional population-based Canadian study observed a slightly higher but nonsignificant increase in diabetes incidence in children during the pandemic, which may have resulted from delays in diagnosis during the pandemic with a catch-up effect (114). There have been several publications on the risk of diabetic ketoacidosis (DKA) during the pandemic. A German diabetes prospective study using registry data of children and adolescents found an increase in type 1 diabetes in the first 3 months of the first wave, and the frequency of DKA at presentation was significantly higher than those for 2019 (44.7% vs. 24.5%, adjusted RR 1.84) and 2018 (vs. 24.1%, adjusted RR 1.85) as well as the proportion with severe DKA (115). A larger study using national data in England during the first two waves found that rates of DKA were higher than those for preceding years across all pandemic periods studied (116). The study reported lower DKA hospital admissions in people with type 1 diabetes but higher rates of DKA in people with type 1 diabetes and those newly diagnosed with diabetes.

There is also evidence of adverse effects of COVID-19 on behavioral health (117) and health-promoting lifestyles during the pandemic. Some small studies in people with diabetes have reported longer-term psychological impact of SARS-CoV-2 infection, including fatigue and risk of suicide (118). Longitudinal follow-up of the Action for Health in Diabetes (Look AHEAD) study of older adults with type 2 diabetes reported a 1.6-fold higher prevalence for depressive symptoms and 1.8-fold higher prevalence for loneliness during the pandemic compared with prepandemic levels (119). Furthermore, many people with diabetes remain fearful of face-to-face contact due to the possible threat from mutant strains of coronavirus (120). Negative emotions due to the pandemic, including lockdowns, have been associated with reduced motivation, physical inactivity, and sedentary behavior (121). Higher levels of pandemic-related distress have been linked to higher A1C (122). Greater pandemic-related life disruptions have been related to higher distress in parents of youth with diabetes, which may have impacted families from racial and ethnic minority groups to a greater degree than non-Hispanic White families (123). On the other hand, for some youth with type 1 diabetes, increased time at home during the early phases of the COVID-19 pandemic provided opportunities for enhanced family support for diabetes self-management and reduced diabetes-related distress (124).

As we recover from the pandemic, it is essential that we prioritize the highest-risk groups for their routine review and assessment as well as management of their behavioral health and risk factors. Diabetes professional bodies in some countries have published guidance on risk stratification and who to prioritize for diabetes review (125,126). Factors to consider for prioritization should include demographics, socioeconomic status, education levels, established complications, comorbidities, and modifiable risk factors, which are associated with high risk of progression of diabetes-related complications.

Several pharmacoepidemiologic studies have examined the association between glucose-lowering medications and risk of COVID-19 and have reported conflicting findings, although most studies showed a lower risk of mortality with metformin and a higher risk in people on insulin. However, the absolute differences in the risks have been small, and these findings could be due to confounding by indication (127). The gold standard for assessing the effects of therapies is by randomized controlled trial (RCT), and only one RCT, the Dapagliflozin in Patients with Cardiometabolic Risk Factors Hospitalized with COVID-19 (DARE-19), a double-blind, placebo-controlled RCT in people with and without type 2 diabetes with at least one cardiovascular risk factor, has been reported (128). In this study, dapagliflozin was well tolerated and resulted in fewer events of organ dysfunction, but results were not statistically significant for the dual primary outcome of prevention (time to new or worsening organ dysfunction or death) and the hierarchical composite outcome of recovery by 30 days.

It is therefore important that people with diabetes have regular SARS-CoV-2 vaccines (see IMMUNIZATIONS, above, for detailed information on COVID-19 vaccines).

It is unclear currently how often people with diabetes will require booster vaccines. Although limited data are available on COVID-19 vaccination attitudes or uptake in people with diabetes in the U.S. (129), diabetes health care professionals may be in a position to address questions and concerns among people with diabetes and encourage vaccination.

Disability

Recommendation

4.22 An assessment of disability should be performed at each visit for people with diabetes. If a disability is impacting functional ability or capacity to manage their diabetes, a referral should be made to an appropriate health care professional specializing in disability (e.g., physical medicine and rehabilitation specialist, physical therapist, occupational therapist, speech-language pathologist). **E**

A disability is defined as a physical or mental impairment that substantially limits one or more major life activities of an individual (130,131). Activities of daily living (ADLs) and instrumental activities of daily living (IADLs) comprise basic and complex life care tasks, respectively. The capacity to accomplish such tasks serves as an important measure of function. Diabetes is associated with a strong increase in the risk of physical disability, with estimates of the association between diabetes and disability representing up to a 50–80% increased risk of disability for people with diabetes compared with people without diabetes (132). Reviews have shown that lower-body functional limitation was the most prevalent disability (47–84%) among people with diabetes (133,134). In a systematic review and meta-analysis, the presence of diabetes increased the risk of mobility disability (15 studies; odds ratio [OR] 1.71 [95% CI 1.53–1.91]; RR 1.51 [95% CI 1.38–1.64], of IADL disability (10 studies; OR 1.65 [95% CI 1.55–1.74]), and of ADL disability (16 studies; OR 1.82 [95% CI 1.63–2.04]; RR 1.82 [95% CI 1.40–2.36]) (132). Diabetic peripheral neuropathy is a common complication of both type 1 and 2 diabetes and may cause impaired postural balance and gait kinematics (135), leading to functional disability. Furthermore, diabetic peripheral neuropathy may progress to cause debilitating neuropathic pain and nontraumatic lower-limb amputation, which has a devastating effect on quality of life (136). In addition to complications of diabetes from microvascular conditions such as diabetic kidney disease, retinopathy, and peripheral neuropathy, it is important to recognize the disabilities caused by macrovascular complications of diabetes. These macrovascular complications, which include coronary heart disease, stroke, and peripheral arterial disease, can lead to further impairments (133).

An assessment of disability should be performed at each visit and a referral made to an appropriate health care professional specializing in disability (e.g., physical medicine and rehabilitation physician, physical therapist, occupational therapist, or speech-language pathologist). Customized rehabilitation interventions for individuals with a disability from diabetes can recover function, allowing for safe physical activity (137), and improve quality of life (138). Additionally, frailty is commonly associated with diabetes, with progression to disability, morbidity, and mortality in older adults. People with diabetes as well as frailty or disability may contend with comorbid conditions such as hypoglycemia, sarcopenia, falls, and cognitive dysfunction. A thorough medical evaluation is imperative to identify the best approaches to preventative and therapeutic interventions with respect to frailty and diabetes management (139).

Moreover, when treating people with an acquired disability from diabetes, it is vital to consider social determinants of health, race/ethnicity, and socioeconomic status (140). Rates of diabetes-related major amputations have been found to be higher in individuals who are from racial and ethnic minority groups (141), live in rural areas, and are from the lowest socioeconomic regions (142). Addressing the complex challenges faced by individuals with acquired disabilities from diabetes requires a multifaceted approach involving solutions from both within and outside the health care system. By focusing on social determinants of health, health care professionals can develop targeted interventions and establish support systems that cater to the specific needs of this population.

Hepatitis C

Infection with hepatitis C virus (HCV) is associated with a higher prevalence of type 2 diabetes, which is present in up to one-third of individuals with chronic HCV infection. HCV may impair glucose metabolism by several mechanisms, including directly via viral proteins and indirectly by altering proinflammatory cytokine levels (143). The use of newer direct-acting antiviral drugs produces a sustained virological response (cure) in nearly all cases and has been reported to improve glucose metabolism in individuals with diabetes (144). A meta-analysis of mostly observational studies found a mean reduction in A1C levels of 0.45% (95% CI −0.60 to −0.30) and reduced requirement for glucose-lowering medication use following successful eradication of HCV infection (145).

Hyperglycemia

In individuals with diabetes, higher A1C level is associated with lower cognitive function (43,146). A meta-analysis of randomized trials found that tight glycemic control, compared with higher A1C goals, was associated with a slightly lower rate of cognitive decline (147). However, these findings were driven by an older study with an A1C goal of $<$7.0% in the tight-control arm. Analyses within the ACCORD, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies found that tight glycemic control (targeting A1C $<$6.0–6.5%) resulted in no differences in cognitive outcomes compared with standard control (147–149). Therefore, intensive glycemic control should not be advised for the improvement of cognitive function in individuals with type 2 diabetes. Additionally, people with type 2 diabetes and dementia are at heightened risk for experiencing hyperglycemic crises (diabetic ketoacidosis and hyperglycemic hyperosmolar state) compared with people without dementia (150), underscoring the importance of supporting diabetes management for individuals experiencing cognitive decline and diminished capacity for self-care.

Hypoglycemia

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycemia. Multiple observational studies of adults with diabetes have found an association between severe hypoglycemic episodes and cognitive decline or incident dementia (151–155). Decreased cognitive function also increases the risk for severe hypoglycemia, likely through impaired ability to recognize and respond appropriately to hypoglycemic symptoms (152,156,157). Tailoring glycemic therapy and/or liberalizing A1C goals may prevent hypoglycemia in individuals with cognitive dysfunction. See Section 13, “Older Adults,” for more detailed discussion of hypoglycemia in older people with type 1 and type 2 diabetes.

Low Testosterone in Men

Recommendation

4.23 In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity or erectile dysfunction, consider screening with a morning serum testosterone level. **B**

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder (158,159). Testosterone replacement in men with symptomatic hypogonadism may have benefits, including improved sexual function, well-being, muscle mass and strength, and bone density (160). In men with diabetes who have symptoms or signs of low testosterone (hypogonadism), a morning total testosterone level should be measured using an accurate and reliable assay (161). In men who have total testosterone levels close to the lower limit, it is reasonable to determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, sex hormone binding globulin, and albumin concentrations (161). Please see the Endocrine Society clinical practice guideline for detailed recommendations (161). Further tests (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to further evaluate the individual. Testosterone replacement in older men with hypogonadism has been associated with increased coronary artery plaque volume, with no conclusive evidence that testosterone supplementation is associated with increased cardiovascular risk in hypogonadal men (161). Erectile dysfunction is common in people with diabetes and warrants evaluation (162).

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Screening

Recommendations

4.24a Adults with type 2 diabetes or prediabetes, particularly those with obesity or cardiometabolic risk factors or established cardiovascular disease, should be screened/risk stratified for clinically significant liver fibrosis (defined as moderate fibrosis to cirrhosis) using a calculated fibrosis-4 index (FIB-4) (derived from age, ALT, AST, and platelets [mdcalc.com/calc/2200/fibrosis4-fib-4-index-liver-fibrosis]), even if they have normal liver enzymes. **B**

4.24b Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for $>$6 months and low FIB-4 should be evaluated for other causes of liver disease. **B**

4.25 Adults with type 2 diabetes or prediabetes with an indeterminate or high FIB-4 should have additional risk stratification by liver stiffness measurement with transient elastography or the blood biomarker enhanced liver fibrosis (ELF). **B**

4.26 Adults with type 2 diabetes or prediabetes with indeterminate results or at high risk for significant liver fibrosis (i.e., by FIB-4, liver stiffness measurement, or ELF) should be referred to a gastroenterologist or hepatologist for further workup. Interprofessional care is recommended for long-term management. **B**

Nonalcoholic fatty liver disease (NAFLD) includes a broad spectrum of disease, ranging from macrovesicular hepatic steatosis (with or without mild inflammation) to nonalcoholic steatohepatitis (NASH) to cirrhosis. This is in the absence of ongoing or recent consumption of significant amounts of alcohol (defined as ingestion of $>$21 standard drinks per week in men and $>$14 standard drinks per week in women over a 2-year period preceding evaluation) or other secondary causes of hepatic steatosis (163).

Diabetes is a major risk factor for developing NASH, disease progression, and worse liver outcomes (164). Recent studies in adults in the U.S. estimated that NAFLD is prevalent in $>$70% of people with type 2 diabetes (165–167). This is consistent with studies from other countries (168). NASH is defined histologically as having $\geq$5% hepatic steatosis and is associated with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis (163). Steatohepatitis is estimated to affect more than half of people with type 2 diabetes with NAFLD (169) and appears to be a driver for the development of fibrosis. Fibrosis stages are classified histologically as the following: F0, no fibrosis; F1, mild; F2, moderate (significant); F3, severe (advanced); and F4, cirrhosis. In the U.S., between 12 and 20% of people with type 2 diabetes have clinically significant fibrosis ($\geq$F2) (165,166,169), with similar prevalence worldwide (164,168). NASH is a leading cause of hepatocellular carcinoma (HCC) (170,171) and of liver transplantation in the U.S., with transplant waiting lists being overrepresented by people with type 2 diabetes (172). Clinicians underestimate its prevalence and do not consistently implement appropriate screening strategies, thus missing the diagnosis of the potentially progressive form of NAFLD in high-risk groups, such as those having obesity or type 2 diabetes. This pattern of underdiagnosis is compounded by sparse referral to specialists and inadequate prescription of medications with proven efficacy in NASH (173,174).

Metabolic dysfunction–associated steatotic liver disease (MASLD) has been proposed to replace the term nonalcoholic fatty liver disease (NAFLD) to identify steatotic liver disease in the presence of at least one cardiometabolic risk factor associated with insulin resistance (e.g., prediabetes, diabetes, atherogenic dyslipidemia, or hypertension) without other identifiable causes of steatosis (175). A separate category outside of MASLD, named metabolic dysfunction and alcoholic liver disease (MetALD), was created for circumstances in which alcohol intake is greater than that allowed for NAFLD but less than that attributed to alcoholic liver disease. The new definition of NAFLD aims to remove potential stigma from the term “fatty” when referring to steatosis and to provide a positive diagnosis by means of having a cardiometabolic risk factor as a surrogate for insulin resistance, the metabolic dysfunction believed to be driving the development of steatosis. While the definition may not conflict with the past definition of NAFLD for people with prediabetes or type 2 diabetes (who already have, by definition, one cardiometabolic risk factor), limitations include the need for better validation, as cardiometabolic risk factors may carry different weights and thus some may also have lower specificity as surrogates for insulin resistance (e.g., hypertension). In addition, some people may have insulin resistance and steatosis without cardiometabolic risk factors, something more common in young adults in primary care clinics or even in some lean people with steatohepatitis. Finally, some people with type 2 diabetes or other forms of diabetes may have steatosis with predominantly insulin secretion deficiency, making diabetes a more questionable surrogate for insulin resistance.

The goal of screening for NAFLD is to identify people at risk for adverse health outcomes associated with NASH, such as cirrhosis, HCC, and death from liver disease. This risk is higher in people who have central obesity and cardiometabolic risk factors or insulin resistance, are >50 years of age, and/or have persistently elevated plasma aminotransferases (AST and/or ALT >30 units/L for >6 months) (176,177). Some genetic variants that alter hepatocyte triglyceride metabolism may also increase the risk of NASH progression and cirrhosis (178,179), amplifying the impact of obesity, but the role of genetic testing in clinical practice remains to be established.

Individuals with clinically significant fibrosis (≥F2), especially those with type 2 diabetes, have a greater risk of cirrhosis with liver decompensation, HCC, liver transplantation, and all-cause mortality (180–183). Increased mortality associated with NAFLD is attributable not only to cirrhosis and HCC but also to extrahepatic cancer (171), type 2 diabetes (184), and cardiovascular disease (185,186). The estimated relative impact depends on length of follow-up and population studied, among other factors. Emerging evidence suggests that NAFLD increases the risk of chronic kidney disease, particularly when liver fibrosis is present (187,188), although the association of NAFLD with diabetic retinopathy is less clear (189). Early diagnosis is essential to prevent future cirrhosis and complications.

A recent meta-analysis reported a prevalence of NAFLD of 22% in people with type 1 diabetes (190). This risk may be linked to the fact that about one-third of people with type 1 diabetes in the U.S. have obesity (191). However, there is large variability in NAFLD prevalence across studies, and most measured liver fat by ultrasound. In one of the few studies using the gold-standard MRI technique to quantify liver fat, the prevalence of steatosis in a population with type 1 diabetes with low prevalence of obesity was only 8.8% compared with 68% in people with type 2 diabetes (192). The prevalence of fibrosis was not established in that study. Therefore, screening for fibrosis in people with type 1 diabetes should only be considered in the presence of additional risk factors for NAFLD, such as obesity, incidental hepatic steatosis on imaging, or elevated plasma aminotransferases.

There is consensus that the fibrosis-4 index (FIB-4) is the most cost-effective strategy for the initial screening of people with prediabetes and cardiometabolic risk factors or with type 2 diabetes in primary care and diabetes clinical settings (168,174,176,177,193–195). See the proposed diagnostic algorithm by an expert group that included ADA representatives in **Fig. 4.2** (174). A screening strategy based on elevated plasma aminotransferases >40 units/L would miss most individuals with NASH in these settings, as clinically significant fibrosis (≥F2) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L (165–167,169,196,197). The American College of Gastroenterology considers the upper limit of normal ALT levels to be 29–33 units/L for male individuals and 19–25 units/L for female individuals (198), as higher levels are associated with increased liver-related mortality, even in the absence of identifiable risk factors. The FIB-4 estimates the risk of hepatic cirrhosis and is calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count (mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). A value of <1.3 is considered low risk of having advanced fibrosis (F3–F4) and for developing adverse liver outcomes, while >2.67 is considered as having a high probability of advanced fibrosis (F3–F4) and increased risk of adverse liver outcomes. FIB-4 predicts changes over time in hepatic fibrosis (199,200) and allows risk stratification of individuals in terms of future liver-related morbidity and mortality (201). FIB-4 has reasonable specificity but low sensitivity, hence a negative result rules out fibrosis while a positive result requires confirmatory testing (200,202–205). It has a reasonable specificity and negative predictive value to rule out advanced fibrosis but lacks adequate sensitivity and positive predictive value to establish presence of advanced fibrosis in many cases, which is the reason why people with diabetes often fall in the "indeterminate" (or intermediate) risk group for advanced fibrosis and adverse liver outcomes (when FIB-4 is between 1.3 and 2.67). However, its low cost, simplicity, and good specificity make it the initial test of choice (**Fig. 4.2**). Performance is better in a population with higher prevalence of significant fibrosis (i.e., hepatology clinics) compared with primary care settings. FIB-4 has not been well validated in pediatric populations and does not perform as well in those aged <35 years. In people with diabetes ≥65 years of age, higher cutoffs for FIB-4 have been recommended (1.9–2.0 rather than >1.3) (206,207).

In people with an indeterminate or high FIB-4, additional risk stratification is required with a liver stiffness measurement (LSM) by transient elastography (**Fig. 4.2**) or, if unavailable, by commercial blood fibrosis biomarkers such as the enhanced liver fibrosis (ELF) test (208) or others. Use of a second nonproprietary diagnostic panel is not recommended (i.e., NAFLD fibrosis score and others), as they generally do not perform better than FIB-4 (167,202). Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in NAFLD (176,177,209). An LSM value of <8.0 kPa has a good negative predictive value to exclude advanced fibrosis (≥F3–F4) (210–212) and indicates low risk for clinically significant fibrosis. Given the lack of widespread availability of LSM, the ELF test is a good alternative. Individuals with ELF <7.7 are considered at low risk for adverse outcomes. Such individuals with diabetes can be followed in nonspecialty clinics with repeat surveillance testing every ≥2 years, although the precise time interval remains to be established. If the LSM is >12 kPa, the risk for advanced fibrosis is high and people with diabetes should be referred to the hepatologist (168). FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize specialty referrals (204,209,213–215) (**Fig. 4.2**).

Specialists may order additional tests for fibrosis risk stratification (175–177,

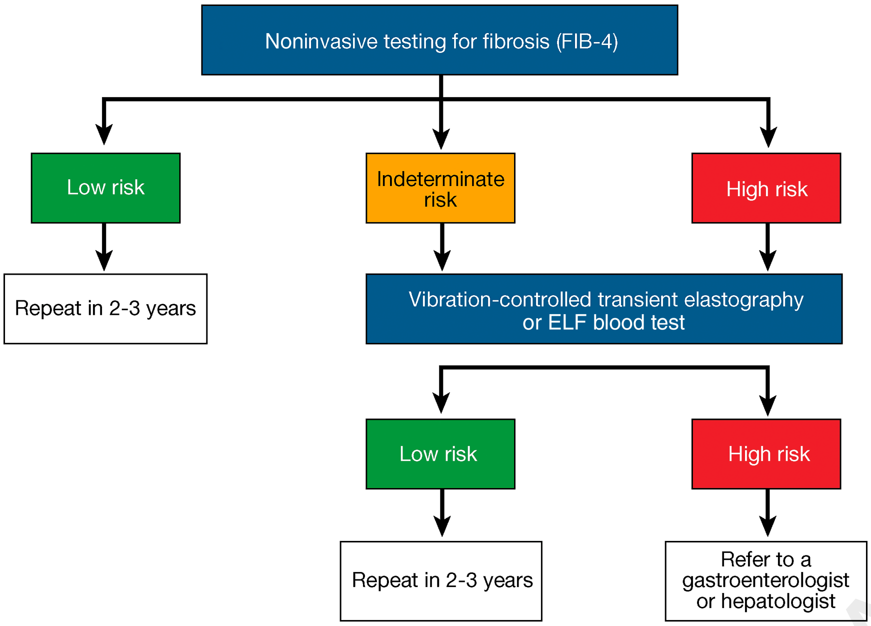

Noninvasive testing for fibrosis (FIB-4)
Low risk
Indeterminate risk
High risk
Repeat in 2-3 years
Vibration-controlled transient elastography or ELF blood test
Low risk
High risk
Repeat in 2-3 years
Refer to a gastroenterologist or hepatologist

Figure 4.2—A proposed algorithm for risk stratification in individuals with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index. Adapted from Kanwal et al. (174).

195,209), with magnetic resonance elastography (MRE) having the best overall performance (particularly for early fibrosis stages). However, the accessibility and costs associated with MRE are barriers to its use. While liver biopsy remains the gold standard for the diagnosis of NASH, its indication is reserved to the discretion of the specialist within an interprofessional team approach due to high costs and potential for morbidity associated with this procedure.

In 2020, an expert panel convened by the American Gastroenterological Association that included representatives of the ADA reviewed the published literature on the burden, screening, risk stratification, diagnosis, and management of individuals with NAFLD (175). See **Fig. 4.2**, which is adapted from this special report (174). A Clinical Care Pathway summarized the diagnosis and management of NAFLD in a subsequent publication (177). Consensus has emerged to start screening with FIB-4 followed by LSM or ELF and patented biomarkers as needed for the noninvasive fibrosis risk stratification of individuals with NAFLD in primary care and diabetes clinics (167,174,176,177,193–195,216).

After initial risk stratification (i.e., FIB-4, LSM, and/or patented biomarkers), people with diabetes at indeterminate or high risk of fibrosis should be referred, based on practice setting, to a gastroenterologist or hepatologist for further workup within the framework of an interprofessional team (163,176,177,216,217).

Management

Recommendations

4.27 Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, with nonalcoholic fatty liver disease (NAFLD) should be recommended lifestyle changes that promote weight loss, ideally within a structured nutrition plan and physical activity program for cardiometabolic benefits **B** and histological improvement. **C**

4.28 For adults with type 2 diabetes, particularly with overweight or obesity, with NAFLD, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated benefits in nonalcoholic steatohepatitis (NASH) as an adjunctive therapy to lifestyle interventions for weight loss. **B**

4.29 Pioglitazone or GLP-1 receptor agonists are the preferred agents for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven NASH or those at high risk with clinically significant liver fibrosis using noninvasive tests. **A**

4.30a In adults with type 2 diabetes and NAFLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 receptor agonists may be continued as clinically indicated, but these therapies lack evidence of benefit in NASH. **B**

4.30b Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis. **C**

4.31a Adults with type 2 diabetes and NAFLD are at increased cardiovascular risk; therefore, comprehensive management of cardiovascular risk factors is recommended. **B**

4.31b Statin therapy is safe in adults with type 2 diabetes and compensated cirrhosis from NAFLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. **B** Statin therapy should be used with caution and close monitoring in people with decompensated cirrhosis, given limited safety and efficacy data. **B**

4.32a Consider metabolic surgery in appropriate candidates as an option to treat NASH in adults with type 2 diabetes **B** and to improve cardiovascular outcomes. **B**

4.32b Metabolic surgery should be used with caution in adults with type 2 diabetes with compensated cirrhosis from NAFLD **B** and is not recommended in decompensated cirrhosis. **B**

While steatohepatitis and cirrhosis occur in lean people with diabetes and are believed to be linked to genetic predisposition, insulin resistance, and environmental factors (218–220), there is ample evidence to implicate excess visceral and overall adiposity in people with overweight and obesity in the pathogenesis of the disease (221,222). Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis (223). Therefore, clinicians should enact evidence-based interventions (as discussed in Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") to promote healthy lifestyle change and weight loss for people with overweight or obesity and NAFLD. A minimum weight loss goal of 5%, preferably ≥10% (224, 225), is needed to improve liver histology, with fibrosis requiring the larger weight reduction to promote change (225–227). Individualized, structured weight loss and exercise programs offer greater benefit than standard counseling in people with NAFLD (218,228).

Dietary recommendations to induce an energy deficit are not different from those for people with diabetes with obesity without NAFLD and should include a reduction of macronutrient content, limiting saturated fat, starch, and added sugar, with adoption of healthier eating patterns. The Mediterranean diet has the best evidence for improving liver and cardiometabolic health (176,193,194, 228–232). Both aerobic and resistance training improve NAFLD in proportion to treatment engagement and intensity of the program (233–235).

Obesity pharmacotherapy may assist with weight loss in the context of lifestyle modification if not achieved by lifestyle modification alone (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

At present, there are no FDA-approved drugs for the treatment of NASH. Therefore, treatment for people with type 2 diabetes and NASH is centered on the dual purpose of treating hyperglycemia and obesity, especially if clinically significant fibrosis ($\geq$F2) is present. The rationale for the treatment of people with type 2 diabetes is based on their high prevalence of NASH with significant fibrosis (10–15% of people with type 2 diabetes) (165–169), their higher risk of disease progression and liver-related mortality (164,183,236), and the lack of pharmacological treatments once cirrhosis is established (237). Therefore, early diagnosis and treatment of NAFLD offers the best opportunity for cirrhosis prevention. Pioglitazone and some glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been shown to be effective to treat steatohepatitis (176, 177,238–240) and may slow fibrosis progression (241–243) and decrease cardiovascular disease (177,239), which is the number one cause of death in people with type 2 diabetes and NAFLD (185).

Pioglitazone improves glucose and lipid metabolism and reverses steatohepatitis in people with prediabetes or type 2 diabetes (244,245) and even without diabetes (246–248). Fibrosis also improved in some trials (245,247). A meta-analysis (241) concluded that pioglitazone treatment results in resolution of NASH and may improve fibrosis. Pioglitazone may halt the accelerated pace of fibrosis progression observed in people with type 2 diabetes (242) and is overall cost-effective for the treatment of NASH (249,250). Vitamin E may be beneficial for the treatment of NASH in people without diabetes (246). However, in people with type 2 diabetes, vitamin E monotherapy was found to be negative in a small RCT (242), and it did not seem to enhance pioglitazone's efficacy when used in combination as reported in an earlier trial in this population (245). Pioglitazone causes dose-dependent weight gain (15 mg/day, mean of 1–2%; 45 mg/day, 3–5%), increases fracture risk, may promote heart failure if used in individuals with preexisting congestive heart failure, and may increase the risk of bladder cancer, although this remains controversial (163,176,177,239,240).

GLP-1 RAs are effective at inducing weight loss and ameliorating elevated plasma aminotransferases and steatosis (238). However, there are only two RCTs of GLP-1 RAs in biopsy-proven individuals with NASH. A small RCT reported that liraglutide improved some features of NASH and, of particular relevance, delayed the progression of fibrosis (251). More recently, once-daily subcutaneous semaglutide in 320 people with biopsy-proven NASH (62% having type 2 diabetes) reported resolution of steatohepatitis in 59% at the higher dose (equivalent to 2.4 mg/week semaglutide) compared with 17% in the placebo group ($P < 0.001$) (243). Cumulatively, semaglutide did not significantly affect the stage of liver fibrosis in this group of people (70% of whom had F2 or F3 at baseline), but it significantly slowed over 72 weeks the progression of liver fibrosis (4.9% with the GLP-1 RA at the highest dose compared with 18.8% on placebo). Tirzepatide (252), sodium–glucose cotransporter inhibitors (253–255), and insulin (240) reduce hepatic steatosis, but their effects on steatohepatitis remain unknown. The use of glucose-lowering agents other than pioglitazone or GLP-1 RAs may be continued in individuals with type 2 diabetes and NAFLD for glycemic control, as clinically indicated. However, these agents have either failed to improve steatohepatitis in paired-biopsy studies (metformin) or have no RCTs with liver histological end points (i.e., sulfonylureas, glitinides, dipeptidyl peptidase 4 inhibitors, or acarbose).

Insulin is the preferred glucose-lowering agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis given the lack of robust evidence about the safety and efficacy of oral agents and noninsulin injectables (i.e., GLP-1 RAs and GLP-1/GIP RAs) (256), although a recent 48-week study suggested that GLP-1 RAs are safe in individuals with NASH and compensated cirrhosis (257).

Metabolic surgery improves NASH and cardiometabolic health, altering the natural history of the disease (258). Meta-analyses report that 70–80% of people have improvement in hepatic steatosis, 50–75% in inflammation and hepatocyte ballooning (necrosis), and 30–40% in fibrosis (259, 260). It may also reduce the risk of HCC (260). Metabolic surgery should be used with caution in individuals with compensated cirrhosis (i.e., asymptomatic stage of cirrhosis without associated liver complications), but with experienced surgeons the risk of hepatic decompensation is similar to that for individuals with less advanced liver disease. Because of the paucity of safety and outcome data, metabolic surgery is not recommended in individuals with decompensated cirrhosis (i.e., cirrhosis stage with complications such as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice) who also have a much higher risk of postoperative development of these liver-related complications (163,176,177).

A number of studies now recognize that adults with type 2 diabetes and NAFLD are at an increased risk of cardiovascular disease and require comprehensive management of cardiovascular risk factors (163,176,177). Within an interprofessional approach, statin therapy should be initiated or continued for cardiovascular risk reduction as clinically indicated. Overall, its use appears to be safe in adults with type 2 diabetes and NASH, including in the presence of compensated cirrhosis (Child-Pugh class A or B cirrhosis) from NAFLD. Some studies even suggest that their use in people with chronic liver disease may reduce episodes of hepatic decompensation and/or overall mortality (261,262). Statin therapy is not recommended in decompensated cirrhosis given limited safety and efficacy data (163,176,177).

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity

(263) (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58% (264,265). In participants with obesity enrolled in the Look AHEAD trial, the prevalence exceeded 80% (266). Individuals with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, and witnessed apnea) should be considered for screening (267). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure management. The evidence for a treatment effect on glycemic control is mixed (268).

Pancreatitis

Diabetes is linked to diseases of the exocrine pancreas, such as pancreatitis, which may disrupt the global architecture or physiology of the pancreas, often resulting in both exocrine and endocrine dysfunction. Up to half of individuals with diabetes may have some degree of impaired exocrine pancreas function (269). People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis (270).

Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of individuals after an episode of acute pancreatitis (271); thus, the relationship is likely bidirectional. Postpancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes (272). Studies of individuals treated with incretin-based therapies for diabetes have also reported that pancreatitis may occur more frequently with these medications, but results have been mixed and causality has not been established (273–275).

Islet autotransplantation should be considered for individuals requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Approximately one-third of individuals undergoing total pancreatectomy with islet autotransplantation are insulin free 1 year postoperatively, and observational studies from different centers have demonstrated islet graft function up to a decade after the surgery in some individuals (276–280). Both person with diabetes and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet autotransplantation.

Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in people with diabetes than in those without and has been associated with higher A1C levels (281–283). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (284,285). In an RCT, intensive periodontal treatment was associated with better glycemic outcomes (A1C 8.3% vs. 7.8% in control subjects and the intensive-treatment group, respectively) and reduction in inflammatory markers after 12 months of follow-up (286).

Sensory Impairment

Hearing impairment, both in high-frequency and low- to midfrequency ranges, is more common in people with diabetes than in those without, with stronger associations found in studies of younger people (287). Proposed pathophysiologic mechanisms include the combined contributions of hyperglycemia and oxidative stress to cochlear microangiopathy and auditory neuropathy (288). In a National Health and Nutrition Examination Survey (NHANES) analysis, hearing impairment was about twice as prevalent in people with diabetes than in those without, after adjusting for age and other risk factors for hearing impairment (289). Low HDL cholesterol, coronary heart disease, peripheral neuropathy, and general poor health have been reported as risk factors for hearing impairment for people with diabetes, but an association of hearing loss with blood glucose levels has not been consistently observed (290). In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, increases in the time-weighted mean A1C was associated with increased risk of hearing impairment when tested after long-term (>20 years) follow-up, with every 10% increase in A1C leading to 19% high-frequency impairment (291). Impairment in smell, but not taste, has also been reported in individuals with diabetes (292).

Statins

Systematic reviews of observational studies and randomized trials have found no adverse effects of statins on cognition (293). The FDA postmarketing surveillance databases have also revealed a low reporting rate for cognitive function–related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications (293). Therefore, fear of cognitive decline should not be a barrier to statin use in people with diabetes when indicated.

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5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: *Standards of Care in Diabetes—2024*

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American Diabetes Association
*Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Building positive health behaviors and maintaining psychological well-being are foundational for achieving diabetes management goals and maximizing quality of life (1,2). Essential to achieving these goals are diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), routine physical activity, counseling and treatment to support cessation of tobacco products and vaping, health behavior counseling, and psychosocial care. Following an initial comprehensive health evaluation (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"), health care professionals are encouraged to engage in person-centered collaborative care with people with diabetes (3–6), an approach that is guided by shared decision-making in treatment plan selection; facilitation of obtaining medical, behavioral, psychosocial, and technology resources and support; and shared monitoring of agreed-upon diabetes care plans and behavioral goals (7,8). Reevaluation during routine care should include assessment of medical and behavioral health outcomes, especially during times of change in health and well-being.

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations

5.1 Strongly encourage all people with diabetes to participate in diabetes self-management education and support (DSMES) to facilitate informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team. **A**

5.2 There are five critical times to evaluate the need for DSMES to promote skills acquisition to aid treatment plan implementation, medical nutrition therapy,

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and well-being: at diagnosis, when not meeting treatment goals, annually, when complicating factors develop (medical, physical, and psychosocial), and when transitions in life and care occur. **E**

5.3 Clinical outcomes, health status, and well-being are key goals of DSMES that should be assessed as part of routine care. **C**

5.4 DSMES should be culturally sensitive and responsive to individual preferences, needs, and values and may be offered in group or individual settings. **A** Such education and support should be documented and made available to members of the entire diabetes care team. **E**

5.5 Consider offering DSMES via telehealth and/or digital interventions to address barriers to access and improve satisfaction. **B**

5.6 Since DSMES can improve outcomes and reduce costs, reimbursement by third-party payers is recommended. **B**

5.7 Identify and address barriers to DSMES that exist at the payer, health system, clinic, health care professional, and individual levels. **E**

5.8 Include social determinants of health of the target population in guiding design and delivery of DSMES **C** with the ultimate goal of health equity across all populations.

The overall objectives of DSMES are to support informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team to improve clinical outcomes, health status, and well-being in a cost-effective manner (2). DSMES services facilitate the knowledge, decision-making, and skills mastery necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes. Health care professionals are encouraged to consider the burden of treatment (9) and the person's level of confidence and self-efficacy for management behaviors as well as the level of social and family support when providing DSMES. An individual's engagement in self-management behaviors and the effects on clinical outcomes, health status, and quality of life, as well as the psychosocial factors impacting the person's ability to self-manage, should be monitored as part of routine clinical care. A randomized controlled trial (RCT) testing a decision-making education and skill-building program (10) showed that addressing these targets improved health outcomes in a population in need of health care resources. Furthermore, following a DSMES curriculum improves quality of care (11).

As the use of judgmental words is associated with increased feelings of shame and guilt, health care professionals are encouraged to consider the impact that language has on building therapeutic relationships and should choose positive, strength-based words and phrases that put people first (4,12). Please see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for more on use of language.

In accordance with the national standards for DSMES (13), all people with diabetes should participate in DSMES, as it helps people with diabetes to identify and implement effective self-management strategies and cope with diabetes (2). Ongoing DSMES helps people with diabetes to maintain effective self-management throughout the life course as they encounter new challenges and as advances in treatment become available (14).

There are five critical time points when the need for DSMES should be evaluated by the health care professional and/or interprofessional team, with referrals made as needed (2):

1. At diagnosis
2. Annually
3. When not meeting treatment goals
4. When complicating factors (e.g., health conditions, physical limitations, emotional factors, or basic living needs) that influence self-management develop
5. When transitions in life and care occur

DSMES focuses on empowering individuals with diabetes by providing them with the tools to make informed self-management decisions (15). DSMES should be person-centered; this is an approach that places the person with diabetes and their family and/or support system at the center of the care model, working in collaboration with health care professionals. Person-centered care is respectful of and responsive to individual and cultural preferences, needs, and values. It ensures that the values of the person with diabetes guide all decision-making (16).

Evidence for the Benefits

DSMES is associated with improved diabetes knowledge and self-care behaviors (17), lower A1C (17–22), lower self-reported weight (23), improved quality of life (19,24,25), reduced all-cause mortality risk (26), positive coping behaviors (5,27), and lower health care costs (28–30). DSMES is associated with an increased use of primary care and preventive services (28,31,32) and less frequent use of acute care and inpatient hospital services (23). People with diabetes who participate in DSMES are more likely to follow best practice treatment recommendations, particularly those with Medicare, and have lower Medicare and insurance claim costs (29,32). Better outcomes were reported for DSMES interventions that were >10 h over the course of 6–12 months (20), included ongoing support (14,33), were culturally (34–36) and age appropriate (37,38), were tailored to individual needs and preferences, addressed psychosocial issues, and incorporated behavioral strategies (15,27,39,40). Individual and group approaches are effective (41–43), with a slight benefit realized by those who engage in both (20).

Strong evidence now exists on the benefits of virtual, telehealth, telephone-based, or internet-based DSMES for diabetes prevention and management in a wide variety of populations and age-groups of people with diabetes (44–56). Technologies such as mobile apps, simulation tools, digital coaching, and digital self-management interventions can also be used to deliver DSMES (57–62). These methods provide comparable or even improved outcomes compared with traditional in-person care (63). Greater A1C reductions are demonstrated with increased engagement (64), although data from trials are considerably heterogeneous.

Technology-enabled diabetes self-management solutions improve A1C most effectively when there is two-way communication between the person with diabetes and the health care team, individualized feedback, use of person-generated health data, and education (47). Continuous glucose monitoring (CGM), when combined with individualized diabetes education or behavioral interventions, has demonstrated greater improvement on glycemic and psychosocial outcomes compared with CGM alone (64,65). Similarly, DSMES plus intermittently scanned CGM has demonstrated increased time in range (70–180 mg/dL [3.9–10.0 mmol/L]), less time above range, and a greater reduction in A1C compared with DSMES alone (66). Incorporating a systematic approach for technology assessment, adoption, and integration into the care plan may help ensure equity in access and standardized application of technology-enabled solutions (www.diabeteseducator.org/danatech/home) (8,31,67–70).

Research supports diabetes care and education specialists (DCES), including nurses (registered nurses and nurse practitioners), registered dietitian nutritionists (RDNs), pharmacists, and other health professionals as providers of DSMES who can also tailor curricula to individual needs (71–73). Members of the DSMES team should have specialized clinical knowledge of diabetes and behavior change principles. In addition, a DCES needs to be knowledgeable about technology-enabled services and may serve as a technology champion within their practice (68). Certification as a DCES (cbdce.org/) and/or board certification in advanced diabetes management (diabeteseducator.org/education/certification/bc_adm) demonstrates an individual's specialized training in and understanding of diabetes management and support (56), and engagement with qualified professionals has been shown to improve diabetes-related outcomes (74). Additionally, there is growing evidence for the role of community health workers (75,76), as well as peer (75–80) and lay leaders (81), in providing ongoing support.

Given individual needs and access to resources, a variety of culturally adapted DSMES programs need to be offered in a variety of settings. The use of technology to facilitate access to DSMES, support self-management decisions, and decrease therapeutic inertia calls for broader adoption of these approaches (82). Additionally, it is important to include social determinants of health (SDOH) of the target population in guiding design and delivery of DSMES. The DSMES team should consider demographic characteristics such as race, ethnic/cultural background, sex/gender, age, geographic location, technology access, education, literacy, and numeracy (56,83). For example, a systematic review and meta-analysis of telehealth DSMES interventions with Black and Hispanic people with diabetes showed a 0.465% decrease in A1C, demonstrating the importance of considering demographic factors in relation to DSMES interventions (53).

Despite the benefits of DSMES, data from the 2017 and 2018 Behavioral Risk Factor Surveillance System of 61,424 adults with self-reported diabetes indicate that only 53% of individuals eligible for DSMES through their health insurance receive it (84). Barriers to DSMES exist at the health system, payer, clinic, health care professional, and individual levels. Low participation may be due to lack of referral or other identified barriers, such as logistical issues (accessibility, timing, and costs) and the lack of a perceived benefit (85). Health system, clinic, programmatic, and payer barriers include lack of administrative leadership support, limited numbers of DSMES professionals, not having a referral to DSMES effectively embedded in the health system service structure, and limited reimbursement rates (86). Thus, in addition to educating referring health care professionals about the benefits of DSMES and the critical times to refer, efforts need to be made to identify and address potential barriers at each level (2). For example, a multilevel diabetes care intervention that combined clinical outreach, standardized protocols, and DSMES with SDOH screening and referrals to social needs support documented a 15% increase in receipt of DSMES, including among people on Medicaid (87). Support from institutional leadership is foundational for the success of DSMES. Expert stakeholders should also support DSMES by providing input and advocacy (56). Alternative and innovative models of DSMES delivery (58) need to be explored and evaluated, including the integration of technology-enabled diabetes and cardiometabolic health services (8,68). One potential model is virtual environments, which allow people with diabetes to self-represent as avatars and interact in a world with embedded informational resources accessed using principles of gamification. An RCT testing DSMES in a virtual environment demonstrated greater weight loss but similar decreases in A1C, blood pressure, cholesterol, and triglycerides compared with DSMES via a standard website (88). Barriers to equitable access to DSMES may be addressed through telehealth delivery of care, virtual environments, and other digital health solutions (56).

Reimbursement

Medicare reimburses DSMES when that service meets the national standards (2,56) and is recognized by the American Diabetes Association (ADA) through the Education Recognition Program (professional.diabetes.org/diabetes-education) or by the Association of Diabetes Care & Education Specialists (diabeteseducator.org/practice/diabetes-education-accreditation-program). DSMES is also covered by most health insurance plans. Ongoing support has been shown to be instrumental for improving outcomes when it is implemented after the completion of education services. Medicare reimburses remote physiologic monitoring for glucose and other cardiometabolic data if certain conditions are met (89). For Medicare Part B, the basics of the DSMES benefit include individual encounters reimbursable for the first 10 h (1 h of individual training and 9 h of group training); if special needs that would interfere with effective group participation are identified on the referral order, individual DSMES encounters are reimbursable for the initial 10 h. For Medicaid, DSMES coverage varies by state.

Although DSMES is frequently reimbursed when performed in person, DSMES can also be provided via telehealth and phone calls (13). These versions may not always be reimbursed; however, changes in reimbursement policies that increase DSMES access and utilization will result in a positive impact on beneficiaries' clinical outcomes, quality of life, health care utilization, and costs (13,90–92). During the time of the coronavirus disease 2019 (COVID-19) pandemic, reimbursement policies were revised (professional.diabetes.org/content-page/dsmes-and-mnt-during-covid-19-national-pandemic), and these changes may provide a new reimbursement paradigm for future provision of DSMES through telehealth channels. Per updated guidance from the Centers for Medicare & Medicaid Services, DSMES telehealth reimbursements remain the same as they were during the public health emergency for most practice settings. Both ADA-recognized and Association of Diabetes Care & Education Specialists–accredited programs were added to the list of approved telehealth professionals via the Consolidated Appropriations Act, 2023. The reimbursement of DSMES telehealth services was extended through the end of 2024. Importantly, DSMES is paid on the physician fee schedule and not the outpatient prospective payment system. Per the Consolidated Appropriations Act, 2023, distant-site health care professionals may be able to bill DSMES as a Medicare telehealth service through 31 December 2024.

MEDICAL NUTRITION THERAPY

When the first ADA Standards of Care guidelines were published in 1989, nutrition was mentioned in two sentences in the entire 4-page document (93). Even now, in 2024, the science of nutrition for diabetes continues to evolve. At the same time, there has been change of emphasis from nutrients (macronutrients and micronutrients) to a focus on foods and, more broadly, dietary patterns. This integrative approach aligns with the 2021 American Heart Association dietary guidance to improve cardiovascular health (94), the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (95), the European Association for the Study of Diabetes/ADA type 1 consensus report (96) and type 2 consensus report (97), and the Dietary Guidelines for Americans, 2020–2025 (98). Simply put, people eat food, not nutrients, and nutrient recommendations need to be applied to what people eat. Additionally, macronutrients are not interchangeable entities and vary by nutrient type and quality. As an example, carbohydrates include legumes, whole grains, and fruits and are in the same category as refined grains, but their health effects are very different (99).

For more detailed information on nutrition therapy, please refer to the ADA consensus report on nutrition therapy (73). Contained in the report is an important and often repeated tenet, i.e., there is not a one-size-fits-all eating pattern for individuals with diabetes, and meal planning should be individualized. Nutrition therapy plays an integral role in overall diabetes management, and each person with diabetes should be actively engaged in education, self-management, and treatment planning with the health care team, including the collaborative development of an individualized eating plan (73,100). All health care professionals should refer people with diabetes for individualized MNT provided by an RDN who is knowledgeable and skilled in providing diabetes-specific MNT (101–103) at diagnosis and as needed throughout the life span, similar to DSMES. MNT delivered by an RDN is associated with A1C absolute decreases of 1.0–1.9% for people with type 1 diabetes (104) and 0.3–2.0% for people with type 2 diabetes (104). See **Table 5.1** for specific nutrition recommendations. Because of the progressive nature of type 2 diabetes, behavior modification alone may not be adequate to maintain euglycemia over time. However, after medication is initiated, nutrition therapy continues to be an important component, and RDNs providing MNT in diabetes care should assess and monitor medication changes in relation to the nutrition care plan (73,100).

Goals of Nutrition Therapy for All People With Diabetes

1. To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, to improve overall health and:
   - achieve and maintain body weight goals
   - attain individualized glycemic, blood pressure, and lipid goals
   - delay or prevent the complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and existing barriers to change
3. To maintain the pleasure of eating by providing nonjudgmental messages about food choices while limiting food choices only when indicated by scientific evidence
4. To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

Weight Management

Management and reduction of weight is important for people with type 1 diabetes, type 2 diabetes, or prediabetes with overweight or obesity. To support weight loss and improve A1C, cardiovascular disease (CVD) risk factors, and well-being in adults with overweight/obesity and prediabetes or diabetes, MNT and DSMES services should include an individualized eating plan in a format that results in an energy deficit in combination with enhanced physical activity (73). Lifestyle intervention programs should be intensive and have frequent follow-up to achieve significant reductions in excess body weight and improve clinical indicators. Behavior modification targets include physical activity, calorie restriction, weight management strategies, and motivation. There is strong and consistent evidence that modest, sustained weight loss can delay the progression from prediabetes to type 2 diabetes (103,105,106) (see Section 3, “Prevention or Delay of Diabetes and Associated Comorbidities”) and is beneficial for the management of type 2 diabetes (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”).

In prediabetes, the weight loss goal is 5–7% or higher for reducing risk of progression to type 2 diabetes (107). In conjunction with support for healthy lifestyle behaviors, medication-assisted weight loss can be considered for people at risk for type 2 diabetes when needed to achieve and sustain 7–10% weight loss (108,109) (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”). People with prediabetes at a healthy weight should also be considered for behavioral interventions to help establish routine aerobic and resistance exercise (107,110,111) as well as to establish healthy eating patterns. Services delivered by health care professionals familiar with diabetes and its management, such as an RDN, have been found to be effective (102).

For many individuals with overweight and obesity with type 2 diabetes, 5% weight loss is needed to achieve beneficial outcomes in glycemic control, lipids, and blood pressure (112,113). It should be noted, however, that the clinical benefits of weight loss are progressive, and more intensive weight loss goals (i.e., 15%) may be appropriate to maximize benefit depending on need, feasibility, and safety (114,115). Long-term durability of weight loss remains a challenge; however, newer medications (beyond metabolic surgery) may have potential for sustainability, impact on cardiovascular outcomes, and weight reduction beyond 10–15% (116–120).

In select individuals with type 2 diabetes, an overall healthy eating plan that results in energy deficit in conjunction with weight loss medications and/or metabolic surgery should be considered to help achieve weight loss and maintenance goals, lower A1C, and reduce CVD risk (108,121,122). Overweight and obesity are also increasingly prevalent in people with type 1 diabetes and present clinical challenges regarding diabetes treatment

Table 5.1—Medical nutrition therapy recommendations

	Recommendations
Effectiveness of nutrition therapy	**5.9** An individualized medical nutrition therapy program as needed to achieve treatment goals, provided by a registered dietitian nutritionist, preferably one who has comprehensive knowledge and experience in diabetes care, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus. A **5.10** Because diabetes medical nutrition therapy can result in cost savings B and improved cardiometabolic outcomes, A medical nutrition therapy should be adequately reimbursed by insurance and other payers. E
Energy balance	**5.11** For all people with overweight or obesity, behavioral modification to achieve and maintain a minimum weight loss of 5% is recommended. A
Eating patterns and macronutrient distribution	**5.12** For diabetes prevention and management of people with prediabetes or diabetes, recommend individualized meal plans that keep nutrient quality, total calories, and metabolic goals in mind, B as data do not support a specific macronutrient pattern. **5.13** Food-based dietary patterns should emphasize key nutrition principles (inclusion of nonstarchy vegetables, whole fruits, legumes, whole grains, nuts/seeds, and low-fat dairy products and minimizing consumption of meat, sugar-sweetened beverages, sweets, refined grains, and ultraprocessed foods) in people with prediabetes and diabetes. B **5.14** Consider reducing overall carbohydrate intake for adults with diabetes to improve glycemia, as this approach may be applied to a variety of eating patterns that meet individual needs and preferences. B
Carbohydrates	**5.15** Emphasize minimally processed, nutrient-dense, high-fiber sources of carbohydrate (at least 14 g fiber per 1,000 kcal). B **5.16** People with diabetes and those at risk are advised to replace sugar-sweetened beverages (including fruit juices) with water or low-calorie or no-calorie beverages as much as possible to manage glycemia and reduce risk for cardiometabolic disease B and minimize consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choices. A **5.17** Provide education on the glycemic impact of carbohydrate, A fat, and protein B tailored to an individual's needs, insulin plan, and preferences to optimize mealtime insulin dosing. **5.18** When using fixed insulin doses, individuals should be provided with education about consistent patterns of carbohydrate intake with respect to time and amount while considering the insulin action time, as it can result in improved glycemia and reduce the risk for hypoglycemia. B
Protein	**5.19** For people with type 2 diabetes, consider avoiding carbohydrate sources high in protein when treating or preventing hypoglycemia, as ingested protein appears to increase insulin response without increasing plasma glucose concentrations. B
Dietary fat	**5.20** Counsel people with diabetes to consider an eating plan emphasizing elements of a Mediterranean eating pattern, which is rich in monounsaturated and polyunsaturated fats and long-chain fatty acids such as fatty fish, nuts, and seeds, to reduce cardiovascular disease risk A and improve glucose metabolism. B
Micronutrients and herbal supplements	**5.21** Dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) are not recommended for glycemic benefits. Health care professionals should inquire about intake of supplements and counsel as needed. C **5.22** Counsel against β-carotene supplementation, as there is evidence of harm for certain individuals and it confers no benefit. B
Alcohol	**5.23** Advise adults with diabetes who consume alcohol to not exceed the recommended daily limits (one drink per day for adult women and two drinks per day for adult men). C Advise abstainers to not start to drink, even in moderation, solely for the purpose of improving health outcomes. C **5.24** Educating people with diabetes about the signs, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially when using insulin or insulin secretagogues, is recommended. The importance of monitoring glucose after drinking alcoholic beverages to reduce hypoglycemia risk should be emphasized. B
Sodium	**5.25** Counsel people with diabetes to limit sodium consumption to $<$2,300 mg/day. B
Nonnutritive sweeteners	**5.26** Counsel people with prediabetes and diabetes that water is recommended over nutritive and nonnutritive sweetened beverages. However, the use of nonnutritive sweeteners as a replacement for sugar-sweetened products in moderation is acceptable if it reduces overall calorie and carbohydrate intake. B

and CVD risk factors (123,124). Sustaining weight loss can be challenging (112,125) but has long-term benefits; maintaining weight loss for 5 years is associated with sustained improvements in A1C and lipid levels (126). MNT guidance from an RDN with expertise in diabetes and weight management throughout the course of a structured weight loss plan is strongly recommended.

Along with routine medical management visits, people with diabetes and prediabetes should be screened during DSMES and MNT encounters for a history of dieting and past or current disordered eating behaviors. Nutrition therapy should be individualized to help address maladaptive eating behavior (e.g., purging) or compensatory changes in medical treatment plan (e.g., overtreatment of hypoglycemic episodes and reduction in medication dosing to reduce hunger) (73) (see DISORDERED EATING BEHAVIOR, below). Disordered eating, eating disorders, and/or disrupted eating can increase challenges for weight and diabetes management. For example, caloric restriction may be essential for glycemic management and weight maintenance, but rigid meal plans may be contraindicated for individuals who are at increased risk of clinically significant maladaptive eating behaviors (127). If eating disorders are identified during screening with diabetes-specific questionnaires, individuals should be referred to a qualified behavioral health professional (1).

Studies have demonstrated that a variety of eating plans, varying in macronutrient composition, can be used effectively and safely in the short term (1–2 years) to achieve weight loss in people with diabetes. These plans include structured low-calorie meal plans with meal replacements (114,126,128), a Mediterranean eating pattern (129), and low-carbohydrate meal plans with additional support (130,131). However, no single approach has been proven to be consistently superior (73, 132–134), and more data are needed to identify and validate those meal plans that are optimal with respect to long-term outcomes and acceptability. Any approach to meal planning should be individualized, considering the health status, personal and cultural preferences, health goals, ability to sustain the recommendations, and ultimately food access and nutrition security (73).

Food Insecurity and Access

Food insecurity is defined as a lack of consistent access to enough food for an active, healthy life (135). Food insecurity affects 16% of adults with diabetes compared with 9% of adults without diabetes (136). There is a complex bidirectional association between food insecurity and cooccurring diabetes. Food security screening should happen at all levels of the health care system. Any member of the health care team can screen for food insecurity using The Hunger Vital Sign. Households are considered at risk if they answer either or both of the following statements as "often true" or "sometimes true" (compared with "never true") (137):

- "Within the past 12 months, we worried whether our food would run out before we got money to buy more."
- "Within the past 12 months, the food we bought just didn't last, and we didn't have money to get more."

If screening is positive for food insecurity, efforts should be made to make referrals to appropriate programs and resources. For more information on efforts and policy recommendations, see "The Biden-Harris Administration National Strategy on Hunger, Nutrition, and Health" (138).

Eating Patterns and Meal Planning

For an understanding of nutrition and diabetes, it is important to clarify the differences between food patterns, eating plans, and approaches. These are terms that are often used interchangeably, but they are different and relevant in individualizing nutrition care plans (139).

- **Eating pattern(s) or food pattern(s).** The totality of all foods and beverages consumed over a given period of time. An eating pattern can be ascribed to an individual, but it is also the term used in prospective cohort and observational nutrition studies to classify and study nutrition patterns. Examples of eating patterns include Mediterranean style, Dietary Approaches to Stop Hypertension (DASH), low-carbohydrate vegetarian, and plant based (139).
- **Eating/meal plan (historically referred to as a diet).** An individualized guide to help plan when, what, and how much to eat on a daily basis, completed by the person with diabetes and the RDN. The eating plan could incorporate an eating pattern combined with a strategy or method to direct some of the choices. Eating plans are based on the individual's usual eating style.
- **Dietary approach.** Method or strategy to individualize a desired eating pattern and provide a practical tool(s) for developing healthy eating patterns. Examples of dietary approaches include the plate method, carbohydrate choice, carbohydrate counting, and highly individualized behavioral approaches (140).

Evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for people with diabetes. Therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Members of the health care team should complement MNT by providing evidence-based guidance that helps people with diabetes make healthy food choices that meet their individualized needs and improve overall health.

Research confirms that a variety of eating patterns are acceptable for the management of diabetes (73,104,141,142). Until the evidence around benefits of different eating patterns is strengthened, health care professionals should focus on the core dimensions common among patterns: inclusion of nonstarchy vegetables, whole fruits, legumes, whole grains, nuts, seeds, and low-fat dairy products and minimizing consumption of meat, sugar-sweetened beverages, sweets, refined grains, and ultraprocessed foods (143,144).

Evidence for eating patterns has been informed by RCTs, prospective cohort studies, systematic reviews, and network meta-analysis. Those most frequently referenced include Mediterranean, DASH, low-fat, carbohydrate-restricted, vegetarian, and vegan eating patterns. As stated previously, there is insufficient evidence to select one over the other (137,141,142,145–154). Ultimately, ongoing diabetes and nutrition education paired with appropriate support to implement and sustain health behaviors is recommended (103).

Meal Planning

Referral to and ongoing support from an RDN is essential to assess the overall nutrition status of, and to work collaboratively with, the person with diabetes to create a personalized meal plan that coordinates and aligns with the overall lifestyle treatment plan, including physical activity and medication use. Using shared decision-making to collaboratively select a method for how to execute the plan may be part of the nutrition care process.

Dietary Approaches/Methods

Few head-to-head studies have compared different dietary approaches. In a systematic review and meta-analysis of carbohydrate counting versus other forms of dietary advice (standard education, low glycemic index, and fixed carbohydrate quantities), no significant differences were seen in A1C levels compared with standard education (145). In another RCT, a simplified carbohydrate counting tool based on individual glycemic response was noninferior to conventional carbohydrate counting in 85 adults with type 1 diabetes (146). In a randomized crossover trial, carbohydrate counting and qualitative meal size (low, medium, and high carbohydrate) were compared. Time in range was 74% for carbohydrate counting and 70.5% for the quantitative meal size estimates. Noninferiority was not confirmed for the qualitative method (147). Newer technologies (smart phone apps and CGM), including automated insulin delivery, may decrease the need for precise carbohydrate counting and allow for personalized nutrition approaches (148,149).

An RCT found that two meal-planning approaches (diabetes plate method and carbohydrate counting) were effective in helping achieve improved A1C (150). The diabetes plate method is a commonly used visual approach for providing basic meal planning guidance in type 1 and type 2 diabetes. This simple graphic (featuring a 9-inch plate) shows how to portion foods (one-half of the plate for nonstarchy vegetables, one-quarter of the plate for protein, and one-quarter of the plate for carbohydrates). Carbohydrate counting is a more advanced skill that helps plan for and track how much carbohydrate is consumed at meals and snacks. Meal planning approaches should be customized to the individual, including their numeracy (150) and food literacy level. Health numeracy refers to understanding and using numbers and numerical concepts in relation to health and self-management (155). Food literacy generally describes proficiency in food-related knowledge and skills that ultimately impact health, although specific definitions vary across initiatives (151,152).

Intermittent fasting or time-restricted eating as strategies for weight and glucose management have been studied and have gained popularity. Intermittent fasting is an umbrella term that includes three main forms of restricted eating: alternate-day fasting (energy restriction of 500–600 calories on alternate days), the 5:2 diet (energy restriction of 500–600 calories on consecutive or nonconsecutive days with usual intake the other five), and time-restricted eating (daily calorie restriction based on window of time of 8–15 h). Each produces mild to moderate weight loss (3–8% loss from baseline) over short durations (8–12 weeks) with no significant differences in weight loss when compared with continuous calorie restriction (153,154,156,157). A few studies have extended up to 52 weeks and show similar findings (158–162) with diverse populations. Generally, time-restricted eating or shortening the eating window can be adapted to any eating pattern and has been shown to be safe for adults with type 1 or type 2 diabetes (161). People with diabetes who are on insulin and/or secretagogues should be medically monitored during the fasting period (163). Because of the simplicity of intermittent fasting and time-restricted eating, these may be useful strategies for people with diabetes who are looking for practical eating management tools.

Use of partial meal replacements or total meal replacements is an additional tool or strategy for energy restriction. Meal replacements are prepackaged foods (bars, shakes, and soups) that contain a fixed amount of macroutrients and micronutrients. They have been shown to improve nutrient quality and glycemic management and to reduce portion size and consequent energy intake. In a meta-analysis involving 17 studies incorporating both partial and total meal replacements, greater weight loss and improvement in A1C and fasting blood glucose were demonstrated compared with conventional diets (164). Meal replacements have been used in several landmark clinical trials, including Look AHEAD (Action for Health in Diabetes) (165), DiRECT (Diabetes Remission Clinical Trial) (166), and PREVIEW (Prevention of Diabetes Through Lifestyle Intervention and Population Studies in Europe and Around the World) (167), showing partial or total meal replacements can be a potential short-term strategy for weight loss.

Regardless of the eating pattern, meal plan, and/or dietary approach selected, long-term follow-up and support from members of the diabetes care team are needed to optimize self-efficacy and maintain behavioral changes (140).

Chrononutrition is a growing and emerging specialty in the field of nutrition and biology that tries to understand how the timing of food ingestion affects metabolic health (168). Glucose metabolism follows a circadian rhythm through diurnal variation of glucose tolerance, peaking during daylight hours when food is consumed. Some preliminary studies show cardiometabolic benefits when food is consumed earlier (169). Similarly, circadian disruptions found in shift workers increase risk of type 2 diabetes (170). Although more research needs to be done, this evolving area of research may show promise to improve glucose regulation.

Religious Fasting

Although intermittent fasting and time-restricted eating are specific dietary strategies for energy restriction, religious fasting has been practiced for thousands of years and is part of many faith-based traditions. Duration, frequency, and type of fast vary among different religions (171). For example, Jewish people abstain from any intake for ∼24 h during Yom Kippur (172,173). For Muslims, Ramadan fasting lasts for a full month, when abstinence from any food or drink is required from dawn to dusk (174). Individuals with diabetes who fast have an increased risk for hypoglycemia, dehydration, hyperglycemia, and ketoacidosis. Risk can vary depending on the type of diabetes, type of therapy, and presence and severity of diabetes-related complications (175). Health care professionals, including RDNs, certified DCES, and others, should inquire about any religious fasting for people with diabetes and provide education and support to accommodate their choice. Education regarding glucose checking, medication/fluid adjustment, timing and intensity of physical activity, and meal choices pre- and post-fast should be provided (176). Treatment pre- and post-fast should be culturally sensitive and individualized (177). Specific recommendations for diabetes management during Ramadan (175) and Yom Kippur (172) are available.

Carbohydrates

Studies examining the optimal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake is a key strategy in reaching glucose goals in people with type 1 and type 2 diabetes (178, 179).

For people with type 2 diabetes, low-carbohydrate and very-low-carbohydrate eating patterns in particular have been found to reduce A1C and the need for antihyperglycemic medications (139,180–184). Systematic reviews and meta-analyses of RCTs found carbohydrate-restricted eating patterns, particularly those considered low carbohydrate (<26% total energy), were effective in reducing A1C in the short term (<6 months), with less difference in eating patterns beyond 1 year (134,182,185–187). Questions still remain about the optimal degree of carbohydrate restriction and the long-term effects of those meal patterns on CVD. A systematic review and meta-analysis of RCTs investigating the dose-dependent effects of carbohydrate restriction found each 10% decrease in carbohydrate intake had reductions in levels of A1C, fasting plasma glucose, body weight, lipids, and systolic blood pressure at 6 months, but favorable effects diminished and were not maintained at follow-up or at greater than 12 months. This systematic review highlights the metabolic complexity of response to dietary intervention in type 2 diabetes as well as the need to better understand longer-term sustainability and results (188). Part of the challenge in interpreting low-carbohydrate research has been due to the wide range of definitions for a low-carbohydrate eating plan (189,190). Weight reduction was also a goal in many low-carbohydrate studies, which further complicates evaluating the distinct contribution of the eating pattern (48,130,134,188). As studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability (180), it is important to reassess and individualize meal plan guidance regularly for those interested in this approach. Health care professionals should maintain consistent medical oversight and recognize that insulin and other diabetes medications may need to be adjusted to prevent hypoglycemia, and blood pressure will need to be monitored. In addition, very-low-carbohydrate eating plans are not currently recommended for individuals who are pregnant or lactating, children, people who have renal disease, or people with or at risk for disordered eating, and these plans should be used with caution in those taking sodium–glucose cotransporter 2 inhibitors because of the potential risk of ketoacidosis (191–193).

Regardless of the amount of carbohydrate in the meal plan, focus should be placed on high-quality, nutrient-dense carbohydrate sources that are high in fiber and minimally processed. The addition of dietary fiber modulates composition of gut microbiota and increases gut microbial diversity. Although there is still much to be elucidated with the gut microbiome and chronic disease, higher-fiber diets are advantageous (194). Both children and adults with diabetes are encouraged to minimize intake of refined carbohydrates with added sugars, fat, and sodium and instead focus on carbohydrates from vegetables, legumes, fruits, dairy (milk and yogurt), and whole grains. People with diabetes and those at risk for diabetes are encouraged to consume a minimum of 14 g of fiber/1,000 kcal, with at least half of grain consumption being whole, intact grains, according to the Dietary Guidelines for Americans (98). Regular intake of sufficient dietary fiber is associated with lower all-cause mortality in people with diabetes (195,196), and prospective cohort studies have found dietary fiber intake is inversely associated with risk of type 2 diabetes (197–199). The consumption of sugar-sweetened beverages and processed food products with large amounts of refined grains and added sugars is strongly discouraged (98,200,201), as these have the capacity to displace healthier, more nutrient-dense food choices.

The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, often with varying definitions of low- and high-glycemic-index foods (202,203). The glycemic index ranks carbohydrate foods on their postprandial glycemic response, and glycemic load takes into account both the glycemic index of foods and the amount of carbohydrate eaten. Studies have found mixed results regarding the effect of glycemic index and glycemic load on fasting glucose levels and A1C, with one systematic review finding no significant impact on A1C (204) while others demonstrated A1C reductions of 0.15% (202) to 0.5% (190,205).

Individuals with type 1 or type 2 diabetes taking insulin at mealtime should be offered comprehensive and ongoing education about nutrition content and the need to couple insulin administration with carbohydrate intake. For people whose meal schedule or carbohydrate consumption is variable, regular education to increase understanding of the relationship between carbohydrate intake and insulin needs is important. In addition, education on using insulin-to-carbohydrate ratios for meal planning can assist individuals with effectively modifying insulin dosing from meal to meal to improve glycemic management (104,178,206–208). Studies have shown that dietary fat and protein can impact early and delayed postprandial glycemia (209–212), and it appears to have a dose-dependent response (213–216). Results from high-fat, high-protein meal studies highlight the need for additional insulin to cover these meals; however, more studies are needed to determine the optimal insulin dose and delivery strategy. The results from these studies also point to individual differences in postprandial glycemic response; therefore, a cautious approach to increasing insulin doses for high-fat and/or high-protein mixed meals is recommended to address delayed hyperglycemia that may occur after eating (73,217,218). If using an insulin pump, a split bolus feature (part of the bolus delivered immediately, the remainder over a programmed duration of time) may provide better insulin coverage for high-fat and/or high-protein mixed meals (210,219).

The effectiveness of insulin dosing decisions should be confirmed with a structured approach to blood glucose monitoring or CGM to evaluate individual responses and guide insulin dose adjustments. Checking glucose 3 h after eating may help to determine if additional insulin adjustments are required (i.e., increasing or stopping bolus) (210,219,220). Adjusting insulin doses to account for high-fat and/or high-protein meals requires determination of anticipated nutrient intake to calculate the mealtime dose. Food literacy, numeracy, interest, and capability should be evaluated (73). For individuals on a fixed daily insulin schedule, meal planning should emphasize a relatively fixed carbohydrate consumption pattern with respect to both time and amount while considering insulin action. Attention to resultant hunger and satiety cues will also help with nutrient modifications throughout the day (73,221). Commercially available automated insulin delivery systems still require basic diabetes management skills, including carbohydrate counting and understanding of the impact of protein and fat on postprandial glucose response (222).

Protein

There is no evidence that adjusting the daily level of protein intake (typically 1–1.5 g/kg body weight/day or 15–20% of total calories) will improve health, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic management or CVD risk (203,223). Therefore, protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety (224).

Historically, low-protein eating plans were advised for individuals with diabetic kidney disease (DKD) (with albuminuria and/or reduced estimated glomerular filtration rate); however, current evidence does not suggest that people with DKD need to restrict protein to less than the generally recommended protein intake (73). Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which glomerular filtration rate declines and may increase risk for malnutrition (225–227).

Strong evidence suggests higher plant protein intake and replacement of animal protein with plant protein is associated with lower risk of all-cause and cardiovascular mortality in the Women's Health Initiative cohort study (228). A meta-analysis of 13 RCTs showed replacing animal with plant proteins leads to small improvements in A1C and fasting glucose in individuals with type 2 diabetes (229). Plant proteins are lower in saturated fat and support planetary health (230).

Fats

Evidence suggests that there is not an optimal percentage of calories from fat for people with or at risk for diabetes and that macronutrient distribution should be individualized according to the individual's eating patterns, preferences, and metabolic goals (73). The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk, and it is recommended that the percentage of total calories from saturated fats should be limited (98,129,231–233). Multiple RCTs including people with type 2 diabetes have reported that a Mediterranean eating pattern (95,129,234–239) can improve both glycemic management and blood lipids. The Mediterranean eating pattern is based on the traditional eating habits in the countries bordering the Mediterranean Sea. Although eating styles vary by country or culture, they share a number of common features, including consumption of fresh fruits and vegetables, whole grains, beans, and nuts/seeds; olive oil as the primary fat source; low to moderate amounts of fish, eggs, and poultry; and limited added sugars, sugary beverages, sodium, highly processed foods, refined carbohydrates, saturated fats, and fatty or processed meats.

Evidence does not conclusively support recommending n-3 (eicosapentaenoic acid and docosahexaenoic acid) supplements for all people with diabetes for the prevention or treatment of cardiovascular events (73,240,241). In individuals with type 2 diabetes, two systematic reviews with n-3 and n-6 fatty acids concluded that the dietary supplements did not improve glycemic management (203,242). In the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial, when compared with placebo, supplementation with n-3 fatty acids at a dose of 1 g/day did not lead to cardiovascular benefit in people with diabetes without evidence of CVD (243). However, results from the Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT) found that supplementation with 4 g/day of pure eicosapentaenoic acid significantly lowered the risk of adverse cardiovascular events. This trial of 8,179 participants, in which over 50% had diabetes, found a 5% absolute reduction in cardiovascular events for individuals with established atherosclerotic CVD taking a preexisting statin with residual hypertriglyceridemia (135–499 mg/dL [1.52–5.63 mmol/L]) (244). See Section 10, "Cardiovascular Disease and Risk Management," for more information. People with diabetes should be advised to follow the guidelines for the general population for the recommended intakes of saturated fat, dietary cholesterol, and *trans* fat (98). *Trans* fats should be avoided. In addition, as saturated fats are progressively decreased in the diet, they should be replaced with unsaturated fats and not with refined carbohydrates (238).

Sodium

As for the general population, people with diabetes are advised to limit their sodium consumption to $<$2,300 mg/day (73). Restriction to $<$1,500 mg, even for those with hypertension, is generally not recommended (245–247). Sodium recommendations should take into account palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate eating plan (248,249).

Micronutrients and Supplements

Despite lack of evidence of benefit from dietary supplements, consumers continue to take them. Estimates show that up to 59% of people with diabetes in the U.S. use supplements (250). Without underlying deficiency, there is no benefit from herbal or nonherbal (i.e., vitamin or mineral) supplementation for people with diabetes (73,251). Federal law in the U.S. broadly defines dietary supplements as having one or more dietary ingredients, including vitamins, minerals, herbs or other botanicals, amino acids, enzymes, tissues from organs or glands, or extracts of these (252).

Routine antioxidant supplementation (such as vitamins E and C) is not recommended due to lack of evidence of efficacy and concern related to long-term safety. Based on the 2022 U.S. Preventative Services Task Force statement, the harms of β-carotene outweigh the benefits for the prevention of CVD or cancer. β-Carotene was associated with increased lung cancer and cardiovascular mortality risk (253).

In addition, there is insufficient evidence to support the routine use of herbal supplements and micronutrients, such as cinnamon (254), curcumin, vitamin D (255), aloe vera, or chromium, to improve glycemia in people with diabetes (73,256).

Although the Vitamin D and Type 2 Diabetes Study (D2d) prospective RCT and Diabetes Prevention and Active Vitamin D (DPVD) showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (257,258), post hoc analyses and meta-analyses suggest a potential benefit in specific populations (257,259–261).

Further research is needed to define individual characteristics and clinical indicators where vitamin D supplementation may be of benefit.

Metformin is associated with vitamin B12 deficiency per a report from the Diabetes Prevention Program Outcomes Study (DPPOS), which suggests that periodic testing of vitamin B12 levels should be considered in people taking metformin, particularly in those with anemia or peripheral neuropathy (262,263) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"). Consumers can consult the U.S. Food and Drug Administration (FDA) Dietary Supplement Ingredient Directory to locate information about ingredients used in dietary supplements and any action taken by the agency with regard to that ingredient (264).

For special populations, including pregnant or lactating individuals, older adults, vegetarians, and people following very-low-calorie or low-carbohydrate diets, a multivitamin may be necessary (265).

Alcohol

Moderate alcohol intake ingested with food does not have major detrimental effects on long-term blood glucose management in people with diabetes. Risks associated with alcohol consumption include hypoglycemia and/or delayed hypoglycemia (particularly for those using insulin or insulin secretagogue therapies), weight gain, and hyperglycemia (for those consuming excessive amounts) (73,256). People with diabetes should be educated about these risks and encouraged to monitor glucose frequently after drinking alcohol to minimize such risks. People with diabetes can follow the same guidelines as those without diabetes consistent with Dietary Guidelines for Americans, 2020–2025 (98). The available evidence does not support recommending alcohol consumption in people who do not currently drink (266). To reduce risk of alcohol-related harms, adults can choose not to drink or to drink in moderation by limiting intake to ≤2 drinks a day for men or ≤1 drink a day for women (one drink is equal to a 12-oz beer, a 5-oz glass of wine, or 1.5 oz of distilled spirits) (266). There is growing evidence for psychoeducational interventions that may increase knowledge about alcohol use and diabetes, may enhance perceived risks, and may reduce alcohol use among young people with type 1 diabetes (267).

Nonnutritive Sweeteners

The FDA has approved many nonnutritive sweeteners (NNS) for consumption by the general public, including people with diabetes (73,268). However, the safety and role of NNS continue to be sources of concern and confusion for the public (269). This confusion has been heightened with the World Health Organization's conditional recommendation (270) against NNS for weight management, the Cleveland Clinic study on erythritol and its relationship to CVD (271), and the International Agency for Research on Cancer classifying aspartame as a possible carcinogen to humans (272). It should be noted the systematic analysis that informed the World Health Organization recommendation excluded individuals with diabetes. In an editorial from the *Journal of Clinical Investigation*, Nobs and Elinav (273) from the Weizmann Institute described the impact these recent studies have had on the public perception of safety of NNS: "The burden of proof has shifted from a need to prove that NNS are unsafe to a necessity of understanding their potential scope of effects on humans in order to optimize their recommended use by populations at risk."

Despite FDA approval and generally recognized as safe (GRAS) status for NNS, as well as established acceptable daily intake (ADI), questions remain. Implementation and interpretation of human NNS studies are inherently challenging. Each of the sweeteners are their own distinct compounds with different molecular structures, although they are often considered together in studies. Issues of duration of exposure (short or long), different physical forms (packets/powder or in beverages), cardiometabolic health of the host, personalized individual response, presence of other nutrient components, the emerging evidence about the microbiome, and limited RCTs complicate the science (273).

For some people with diabetes who are accustomed to regularly consuming sugar-sweetened products, NNS (containing few or no calories) may be an acceptable substitute for nutritive sweeteners (those containing calories, such as sugar, honey, and agave syrup) when consumed in moderation (274,275). NNS do not appear to have a significant effect on glycemic management (104,276,277), and they can reduce overall calorie and carbohydrate intake (104,274) as long as individuals are not compensating with additional calories from other food sources (73,278). There is mixed evidence from systematic reviews and meta-analyses for NNS use with regard to weight management, with some finding benefit in weight loss (279–281) while other research suggests an association with weight gain (282,283). This may be explained by reverse causality and residual confounding variables (283). The addition of NNS to eating plans poses no benefit for weight loss or reduced weight gain without energy restriction (284). In a recent systematic review and meta-analysis using low-calorie and no-calorie sweetened beverages as an intended substitute for sugar-sweetened beverages, a small improvement in body weight and cardiometabolic risk factors was seen without evidence of harm and had a direction of benefit similar to that seen with water. Health care professionals should continue to recommend water, but people with overweight or obesity and diabetes may also have a variety of no-calorie or low-calorie sweetened products so that they do not feel deprived (285).

Health care professionals should continue to recommend reductions in sugar intake and calories with or without the use of NNS. Assuring people with diabetes that NNS have undergone extensive safety evaluation by regulatory agencies and are continually monitored can allay unnecessary concern for harm. Health care professionals can regularly assess individual use of NNS based on the acceptable daily intake (amount of a substance considered safe to consume each day over a person's life) and recommend moderation. See the chart from the FDA on safe levels of sweeteners found at fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food.

PHYSICAL ACTIVITY

Recommendations

5.27 Counsel youth with type 1 diabetes **C** or type 2 diabetes **B** to engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week.

5.28 Counsel most adults with type 1 diabetes **C** and type 2 diabetes **B** to engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.

5.29 Counsel adults with type 1 diabetes **C** and type 2 diabetes **B** to engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.

5.30 Recommend flexibility training and balance training 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance. **C**

5.31 For all people with diabetes, evaluate baseline physical activity and time spent in sedentary behavior (i.e., quiet sitting, lying, and leaning). For people who do not meet activity guidelines, encourage increase in physical activities (e.g., walking, yoga, housework, gardening, swimming, and dancing) above baseline (type 1 diabetes **E** and type 2 diabetes **B**). Counsel that prolonged sitting should be interrupted every 30 min for blood glucose benefits. **C**

Physical activity is a general term that includes all movement that increases energy use and is an important part of the diabetes management plan. Exercise is a more specific form of physical activity that is structured and designed to improve physical fitness. Both physical activity and exercise are important. Exercise has been shown to improve blood glucose levels, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being (286). Physical activity is as important for those with type 1 diabetes as it is for the general population, but its specific role in the prevention of diabetes complications and the management of blood glucose is not as clear as it is for those with type 2 diabetes. Many individuals with type 2 diabetes do not meet the recommended exercise level per week (150 min). Objective measurement by accelerometer in 871 individuals with type 2 diabetes showed that 44.2%, 42.6%, and 65.1% of White, African American, and Hispanic individuals, respectively, met the recommended threshold of exercise (287). An RCT in 1,366 individuals with prediabetes combined a physical activity intervention with text messaging and telephone support, which showed improvement in daily step count at 12 months compared with the control group. Unfortunately, this was not sustained at 48 months (288). Another RCT, including 324 individuals with prediabetes, showed increased physical activity at 8 weeks with supportive text messages, but by 12 weeks there was no difference between groups (289). It is important for diabetes care management teams to understand the difficulty that many people have reaching recommended treatment goals and to identify individualized approaches to improve goal achievement, which may need to change over time.

Moderate to high volumes of aerobic activity are associated with substantially lower cardiovascular and overall mortality risks in both type 1 and type 2 diabetes (290). A prospective observational study of adults with type 1 diabetes suggested that higher amounts of physical activity led to reduced cardiovascular mortality after a mean follow-up time of 11.4 years for people with and without chronic kidney disease (291). Additionally, structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even without a significant change in BMI (292). There are also considerable data for the health benefits (e.g., increased cardiovascular fitness, greater muscle strength, improved insulin sensitivity) of regular exercise for those with type 1 diabetes (293). Exercise training in type 1 diabetes may also improve several important markers such as triglyceride level, LDL cholesterol, waist circumference, and body mass (294). In adults with type 2 diabetes, higher levels of exercise intensity are associated with greater improvements in A1C and in cardiorespiratory fitness (295); sustained improvements in cardiorespiratory fitness and weight loss have also been associated with a lower risk of heart failure (258). Other benefits include slowing the decline in mobility among overweight people with diabetes (296). The ADA position statement "Physical Activity/Exercise and Diabetes" reviews the evidence for the benefits of exercise in people with type 1 and type 2 diabetes and offers specific recommendations (297). Increased physical activity (soccer training) has also been shown to be beneficial for improving overall fitness in Latino men with obesity, demonstrating feasible methods to increase physical activity in this population (298). Physical activity and exercise should be recommended and prescribed to all individuals who are at risk for or with diabetes as part of management of glycemia and overall health. Specific recommendations and precautions will vary by the type of diabetes, age, activity, and presence of diabetes-related health complications. Recommendations should be tailored to meet the specific needs of each individual (297).

Exercise and Youth

Youth with diabetes or prediabetes should be encouraged to engage in regular physical activity, including at least 60 min of moderate to vigorous aerobic activity every day and muscle- and bone-strengthening activities at least 3 days per week (299). In general, youth with type 1 diabetes benefit from being physically active, and meta-analyses have demonstrated a significant association between physical activity and lower A1C (300). Thus, an active lifestyle should be recommended to all (301). Youth with type 1 diabetes who engage in more physical activity may have better health outcomes and health-related quality of life (302,303). See Section 14, "Children and Adolescents," for details.

Frequency and Type of Physical Activity

For all people with diabetes, evaluate baseline physical activity and time spent in sedentary behavior (quiet sitting, lying, and leaning). For people who do not meet activity guidelines, encourage an increase in physical activity (walking, yoga, housework, gardening, swimming, and dancing) above baseline (304). Health care professionals should counsel people with diabetes to engage in aerobic and resistance exercise regularly (240). Aerobic activity bouts should last at least 10 min, with the goal of ∼30 min/day or more most days of the week for adults with type 2 diabetes. Daily exercise, or at least not allowing more than 2 days to elapse between exercise sessions, is recommended to decrease insulin resistance, regardless of diabetes type (305,306). A study in adults with type 1 diabetes found a dose-response inverse relationship between self-reported bouts of physical activity per week and A1C, BMI, hypertension, dyslipidemia, and diabetes-related complications such as hypoglycemia, diabetic ketoacidosis, retinopathy, and microalbuminuria (307).

Over time, activities should progress in intensity, frequency, and/or duration to at least 150 min/week of moderate-intensity exercise. Adults able to run at 6 miles/h (9.7 km/h) for at least 25 min can benefit sufficiently from shorter durations of vigorous-intensity activity or interval training (75 min/week) (297). Many adults, including most with type 2 diabetes, may be unable or unwilling to participate in such intense exercise and should engage in moderate exercise for the recommended duration. Adults with diabetes are encouraged to engage in 2–3 sessions/week of resistance exercise on nonconsecutive days (308). Although heavier resistance training with free weights or weight machines may improve glycemia and strength (309), resistance training of any intensity is recommended to improve strength, balance, and the ability to engage in activities of daily living throughout the life span. Health care professionals should support people with diabetes to set stepwise goals toward meeting the recommended exercise goals. As individuals intensify their exercise program, medical monitoring may be indicated to ensure safety and evaluate the effects on glucose management. (See PHYSICAL ACTIVITY AND GLYCEMIC MANAGEMENT, below.)

Evidence supports that all individuals, including those with diabetes, should be encouraged to reduce the amount of time spent being sedentary—waking behaviors with low energy expenditure (e.g., seated work at a computer or watching television)—by breaking up bouts of sedentary activity ($>$30 min) by briefly standing, walking, or performing other light physical activities (310,311). Participating in leisure-time activity and avoiding extended sedentary periods may help prevent type 2 diabetes for those at risk and may also aid in glycemic management for those with diabetes (312,313).

A systematic review and meta-analysis found higher frequency of regular leisure-time physical activity was more effective in reducing A1C levels (314). A wide range of activities, including yoga, tai chi, and other types, can have significant impacts on A1C, flexibility, muscle strength, and balance (286,315–317). Flexibility and balance exercises may be particularly important in older adults with diabetes to maintain range of motion, strength, and balance (297) (**Fig. 5.1**). There is strong evidence that exercise interventions in individuals with type 2 diabetes improve depression, A1C, and overall psychosocial well-being (318).

Physical Activity and Glycemic Management

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (297) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (319). If not contraindicated, people with type 2 diabetes should be encouraged to do at least two weekly sessions of resistance exercise (free weights, machines, elastic bands, or body weight as resistance), with each session consisting of at least one set (group of consecutive repetitive exercise motions) of five or more different resistance exercises involving the large muscle groups (320).

For people with type 1 diabetes, although exercise, in general, is associated with improvement in disease status, care needs to be taken in titrating exercise with respect to glycemic management. Each individual with type 1 diabetes has a variable glycemic response to exercise. This variability should be taken into consideration when recommending the type and duration of exercise for a given individual (293).

Individuals of childbearing potential with preexisting diabetes, particularly type 2 diabetes, and those at risk for or presenting with gestational diabetes mellitus should be advised to engage in regular moderate physical activity prior to and during their pregnancies as tolerated (297).

High-Intensity Interval Training

High-intensity interval training (HIIT) is a plan that involves aerobic training done between 65% and 90% VO_{2peak} or 75% and 95% heart rate peak for 10 s to 4 min with 12 s to 5 min of active or passive recovery. HIIT has gained attention as a potentially time-efficient modality that can elicit significant physiological and metabolic adaptations for individuals with type 1 and type 2 diabetes (321,322). Higher intensities of aerobic training are generally considered superior to low-intensity training (323). HIIT showed reductions in A1C and BMI and improvement in fitness levels in individuals with type 2 diabetes. Because HIIT can lead to transient increases in post-exercise hyperglycemia, individuals with type 2 diabetes are encouraged to monitor blood glucose when starting (320). In type 1 diabetes, HIIT is associated with reductions in A1C levels, reduction in insulin requirements, and improvement in cardiometabolic risk profiles (322). Variability in glucose may occur with an increased risk in delayed hypoglycemia, so careful monitoring of glucose during and after HIIT is advised (322).

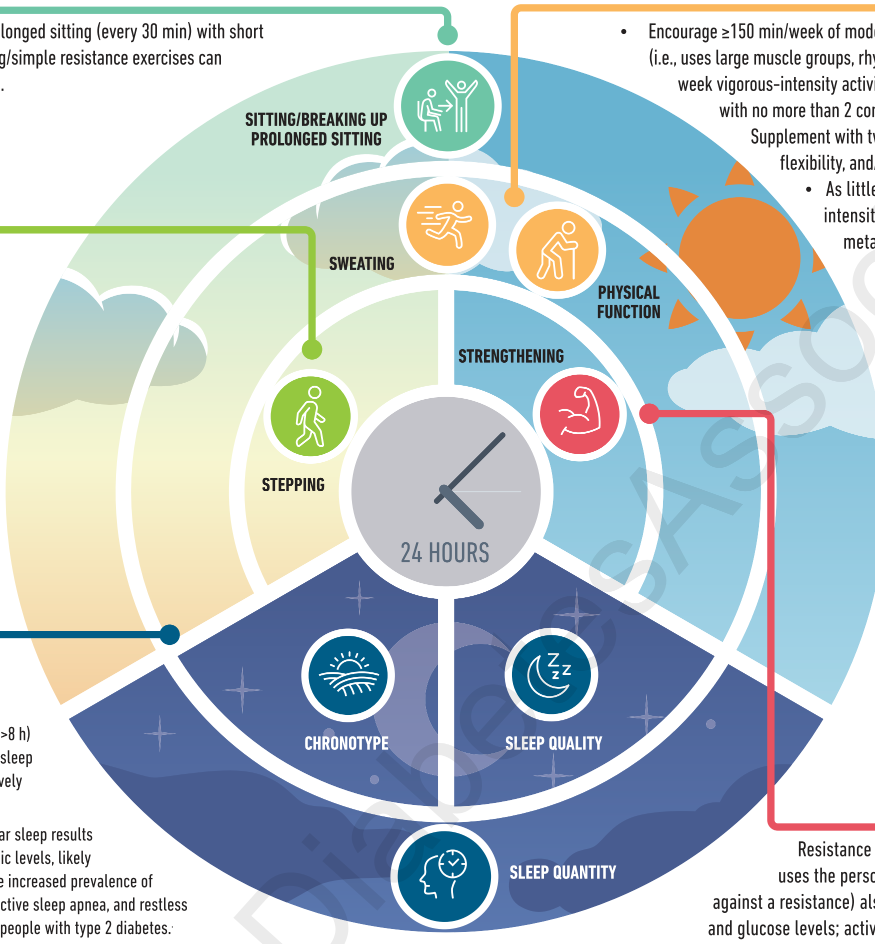
Pre-exercise Evaluation

As discussed more fully in Section 10, "Cardiovascular Disease and Risk Management," the best protocol for assessing asymptomatic people with diabetes for coronary artery disease remains unclear. The ADA consensus report "Screening for Coronary Artery Disease in Patients With Diabetes" (324) concluded that routine testing is not recommended. However, health care professionals should perform a careful history, assess cardiovascular risk factors, and be aware of the atypical presentation of coronary artery disease, such as recent reported or tested decrease in exercise tolerance in people with diabetes. Certainly, those with high risk should be encouraged to start with short periods of low-intensity exercise and slowly increase the duration and intensity as tolerated. Health care professionals should assess for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, untreated proliferative retinopathy, autonomic neuropathy, peripheral neuropathy, balance impairment, and a history of foot ulcers or Charcot foot. Age and previous physical activity level should be considered when customizing the exercise plan to the individual's needs. Those with complications may need a more thorough evaluation prior to starting an exercise program (293).

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity may cause hypoglycemia if the medication dose or carbohydrate consumption is not adjusted for the exercise bout and post-bout impact on glucose. Individuals on these therapies may need to ingest some added carbohydrate if pre-exercise glucose levels are $<$90 mg/dL ($<$5.0 mmol/L), depending on whether they are able to lower insulin doses during the workout (such as with an insulin pump or reduced pre-exercise insulin dosage), the time of day exercise is done, and the intensity

IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIORS FOR TYPE 2 DIABETES



SITTING/BREAKING UP PROLONGED SITTING

Limit sitting. Breaking up prolonged sitting (every 30 min) with short regular bouts of slow walking/simple resistance exercises can improve glucose metabolism.

STEPPING

- An increase of only 500 steps/day is associated with 2–9% decreased risk of cardiovascular morbidity and all-cause mortality.
- A 5- to 6-min brisk-intensity walk per day equates to ~4 years' greater life expectancy.

SLEEP

Aim for consistent, uninterrupted sleep, even on weekends.

Quantity – Long (>8 h) and short (<6 h) sleep durations negatively impact A1C.

Quality – Irregular sleep results in poorer glycemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnea, and restless leg syndrome in people with type 2 diabetes.

Chronotype – Evening chronotypes (i.e., night owl: go to bed late and get up late) may be more susceptible to inactivity and poorer glycemic levels vs. morning chronotypes (i.e., early bird: go to bed early and get up early).

SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)

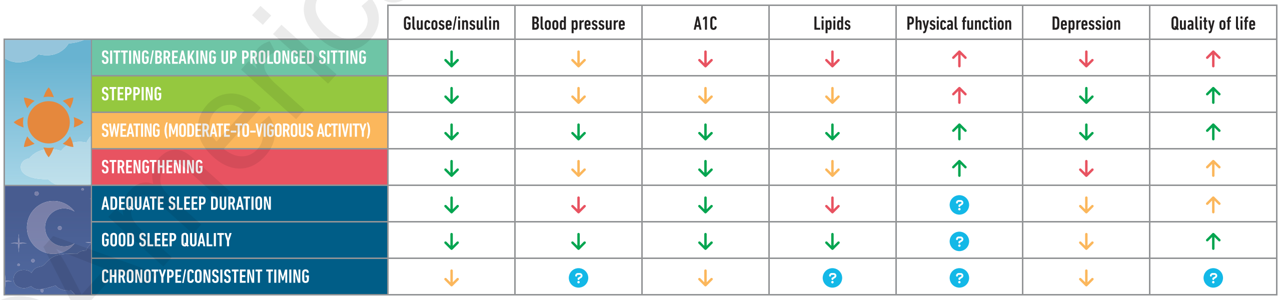
- Encourage ≥150 min/week of moderate-intensity physical activity (i.e., uses large muscle groups, rhythmic in nature) OR ≥75 min/week vigorous-intensity activity spread over ≥3 days/week, with no more than 2 consecutive days of inactivity. Supplement with two to three resistance, flexibility, and/or balance sessions.
- As little as 30 min/week of moderate-intensity physical activity improves metabolic profiles.

Physical function/frailty/sarcopenia

- The frailty phenotype in type 2 diabetes is unique, often encompassing obesity alongside physical frailty, at an earlier age. The ability of people with type 2 diabetes to undertake simple functional exercises in middle age is similar to that in those over a decade older.

STRENGTHENING

Resistance exercise (i.e., any activity that uses the person's own body weight or works against a resistance) also improves insulin sensitivity and glucose levels; activities like tai chi and yoga also encompass elements of flexibility and balance.



	Glucose/insulin	Blood pressure	A1C	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ **Higher levels/improvement** (physical function, quality of life); ↓ **Lower levels/improvement** (glucose/insulin, blood pressure, A1C, lipids, depression); ? no data available;
↑ Green arrows = strong evidence; ↑ Yellow arrows = medium-strength evidence; ↑ Red arrows = limited evidence.

Figure 5.1—Importance of 24-h physical behaviors for type 2 diabetes. Reprinted from Davies et al. (97).

and duration of the activity (293). In some people with diabetes, hypoglycemia after exercise may occur and last for several hours due to increased insulin sensitivity. Hypoglycemia is less common in those who are not treated with insulin or insulin secretagogues, and no routine preventive measures for hypoglycemia are usually advised in these cases. Intense activities may actually raise blood glucose levels instead of lowering them, especially if pre-exercise glucose levels are elevated

(293). Because of the variation in glycemic response to exercise bouts, people with diabetes need to be educated to check blood glucose levels or consult sensor glucose values before and after periods of exercise and about the potential prolonged effects (depending on intensity and duration) (325).

Exercise in the Presence of Microvascular Complications

See Section 11, "Chronic Kidney Disease and Risk Management," and Section 12, "Retinopathy, Neuropathy, and Foot Care," for more information on these long-term complications. A meta-analysis on this topic demonstrated moderate certainty of evidence that high versus low levels of physical activity were associated with lower CVD incidence and mortality (summary risk ratio 0.84 [95% CI 0.77–0.92], n = 7, and 0.62 [0.55–0.69], n = 11) and fewer microvascular complications (0.76 [0.67–0.86], n = 8). Dose-response meta-analyses showed that physical activity was associated with lower risk of diabetes-related complications even at lower levels (326).

Retinopathy

If proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy is present, then vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (327). Consultation with an ophthalmologist prior to engaging in an intense exercise plan may be appropriate.

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities can result in an increased risk of skin breakdown, infection, and Charcot joint destruction with some forms of exercise. Therefore, a thorough assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy. Studies have shown that moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy who use proper footwear (328). In addition, 150 min/week of moderate exercise was reported to improve outcomes in people with prediabetic neuropathy (329). All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non–weight-bearing activities.

Autonomic Neuropathy

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia (330). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (331). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Diabetic Kidney Disease

Physical activity can acutely increase urinary albumin excretion. However, there is no evidence that vigorous-intensity exercise accelerates the rate of progression of DKD, and there appears to be no need for specific exercise restrictions for people with DKD in general (327).

SMOKING CESSATION: TOBACCO, E-CIGARETTES, AND CANNABIS

Recommendations

5.32 Advise all people with diabetes not to use cigarettes and other tobacco products or e-cigarettes. **A**

5.33 As a routine component of diabetes care and education, ask people with diabetes about the use of cigarettes or other tobacco products. After identification of use, recommend and refer for combination treatment consisting of both tobacco/smoking cessation counseling and pharmacological therapy. **A**

A causal link between cigarette smoking and diabetes has been established and reported on by the Surgeon General for over a decade (332). Results from epidemiologic, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and multiple health risks that can have a profound impact on morbidity and mortality for people with diabetes (332). People with diabetes who smoke and are exposed to second-hand smoke have a heightened risk of macrovascular complications (e.g., cardiovascular and peripheral vascular disease), microvascular complications (e.g., kidney disease and visual impairment), worse glycemic outcomes, and premature death compared with those who do not smoke (333–336). Emerging data suggest smoking has a role in the development of type 2 diabetes, and quitting has been shown to significantly decrease this risk over time (337–340).

The routine (every visit with every person), thorough assessment of all types of tobacco use is essential to prevent tobacco product initiation and promote cessation. Evidence demonstrates significant benefits to quitting smoking for all people, resulting in a reduction and even reversal of adverse health effects in addition to an increase in life expectancy by as much as a decade (341). However, data show tobacco use prevalence among adults with chronic conditions has remained persistently higher than that in the general population (342), with recent declines in smoking in middle-aged people with diabetes but not in adolescents and young adults (342). Numerous large RCTs have demonstrated the efficacy and cost-effectiveness of both intensive and brief counseling in smoking cessation, including the use of telephone quit lines and web-based interventions, in reducing tobacco use and maintaining abstinence from smoking (341,343,344). Current recommendations include both counseling and pharmacologic therapy to assist with smoking cessation in nonpregnant adults (345); however, more than two-thirds of people trying to quit do not receive treatment following evidence-based guidelines (341).

Weight gain after smoking cessation has been a concern related to diabetes management and risk for new onset of disease (346). While post-cessation weight gain is an identified issue, studies have found that an average weight gain of 3–5 kg does not necessarily persist long term or diminish the substantial cardiovascular benefit realized from smoking cessation (337). These findings highlight the need for tobacco cessation treatment that addresses eating and physical activity needs. One study in people with newly diagnosed type 2 diabetes who smoke found that smoking cessation was associated with amelioration of microalbuminuria and reduction in blood pressure after 1 year (347).

In recent years, there has been an increase in the use and availability of multiple noncigarette nicotine products. The evidence regarding the effect of these products on diabetes is not as clear as that for combustible cigarettes. It is known that smokeless tobacco products, such as dip and chew, pose an increased risk for CVD (348). E-cigarettes and vaping have gained public awareness and popularity because of perceptions that e-cigarette use is less harmful than regular cigarette smoking (349,350). While combustible tobacco products are clearly the most harmful, electronic products should not be characterized as harmless, as health risks with use that affect the cardiovascular and respiratory systems have been identified (351,352). Individuals with diabetes should be advised to avoid vaping and using e-cigarettes, either as a way to stop smoking combustible cigarettes or as a recreational drug. If people are using e-cigarettes to quit, they should be advised to avoid using both combustible and electronic cigarettes, and if using only e-cigarettes, they should be advised to have a plan to quit these also (344).

Increased legalization and multiple formulations of cannabis products have resulted in increased prevalence in the use of these products in all age-groups (353, 354). Significant increases in tetrahydrocannabinol (THC) concentrations and use of additional psychoactive cannabinoid products, such as delta-8 THC, are of specific concern (355). Most of these products are currently unregulated by the FDA, and public health warnings regarding use have been issued (356). The FDA reports adverse effects related to delta-8 THC, some of which may have health implications for people with diabetes (e.g., vomiting) (356). Evidence of specific increased risk of diabetic ketoacidosis and hyperglycemic ketosis associated with cannabis use and cannabis hyperemesis syndrome in adults with type 1 diabetes has been recently reported (357–359).

Diabetes education programs offer potential to systematically reach and engage individuals with diabetes in smoking cessation efforts. A cluster randomized trial found statistically significant increases in quit rates and long-term abstinence rates (>6 months) when smoking cessation interventions were offered through diabetes education clinics, regardless of motivation to quit at baseline (360). The increased prevalence in use of an expanding landscape of both tobacco and cannabis products and the impact on the health of people with diabetes highlights the need to ask about use of these products, educate individuals regarding the associated risks, and provide support for cessation.

SUPPORTING POSITIVE HEALTH BEHAVIORS

Recommendation

5.34 Behavioral strategies should be used to support diabetes self-management and engagement in health behaviors (e.g., taking medications, using diabetes technologies, and engaging in physical activity and healthy eating) to promote optimal diabetes health outcomes. **A**

Given associations with glycemic outcomes and risk for future complications (361,362), it is important for diabetes care professionals to support people with diabetes to engage in health-promoting behaviors (preventive, treatment, and maintenance), including blood glucose monitoring, taking insulin and medications, using diabetes technologies, engaging in physical activity, and making nutritional changes. Evidence supports using a variety of behavioral strategies and multicomponent interventions to help people with diabetes and their caregivers or family members develop health behavior routines and overcome barriers to self-management behaviors (363–365). Behavioral strategies with empirical support include motivational interviewing (366–368), patient activation (369), goal setting and action planning (368,370–372), problem-solving (371,373), tracking or self-monitoring health behaviors with or without feedback from a health care professional (368,370–372), and facilitating opportunities for social support (368, 371,372). There is mixed evidence about behavioral economics strategies (e.g., financial incentives and exposure to information about social norms) to promote engagement in health behaviors among people with diabetes; such strategies tend to enhance intentions and demonstrate short-term benefits for behavior change, although there is less evidence about sustained effects (374). Multicomponent behavior change intervention packages have the highest efficacy for behavioral and glycemic outcomes (363,372,375). For youth with diabetes, family-based behavioral intervention packages and multisystem interventions that facilitate health behavior change demonstrate benefit for increasing management behaviors and improving glycemic outcomes (364). As with all diabetes health care, it is important to adapt and tailor behavior change strategies to the characteristics and needs of the individual and population (376–378). Health behavior change strategies may be delivered by behavioral health professionals, DCES, other trained health care professionals (370, 379–381), or qualified community health workers (370,371). These approaches may be delivered via digital health tools (372, 380,382). There are effective strategies to train diabetes care professionals to use such methods (e.g., motivational interviewing) (383).

PSYCHOSOCIAL CARE

Recommendations

5.35 Psychosocial care should be provided to all people with diabetes, with the goal of optimizing health-related quality of life and health outcomes. Such care should be integrated with routine medical care and delivered by trained health care professionals using a collaborative, person-centered, culturally informed approach. **A**

5.36 Diabetes care teams should implement psychosocial screening protocols for general and diabetes-related mood concerns as well as other topics such as stress, quality of life, available resources (financial, social, family, and emotional), and/or psychiatric history. Screening should occur at least annually or when there is a change in disease, treatment, or life circumstances. **C**

5.37 When indicated, refer to behavioral health professionals or other trained health care professionals, ideally those with experience in diabetes, for further assessment and treatment for symptoms of diabetes distress, depression, suicidality, anxiety, treatment-related fear of hypoglycemia, disordered eating, and/or cognitive capacities. Such specialized psychosocial care should use age-appropriate standardized and validated tools and treatment approaches. **B**

5.38 Consider developmental factors and use age-appropriate validated tools for psychosocial screening in people with diabetes. **E**

Please refer to the ADA position statement "Psychosocial Care for People With Diabetes" for a list of assessment tools and additional details (1) and the ADA Behavioral Health Toolkit for assessment questionnaires and surveys (professional.diabetes.org/meetings/behavioral-health-toolkit). Throughout the Standards of Care, the broad term "behavioral health" is used to encompass both *1*) health behavior engagement and relevant factors and *2*) behavioral health concerns and care related to living with diabetes.

Complex environmental, social, family, behavioral, and emotional factors, known as psychosocial factors, influence living with type 1 and type 2 diabetes and achieving optimal health outcomes and psychological well-being. Thus, individuals with diabetes and their families are challenged with complex, multifaceted issues when integrating diabetes care into daily life (384). Clinically significant behavioral health diagnoses are considerably more prevalent in people with diabetes than in those without (385–387). Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (57,388–392) or family's (391) ability to carry out diabetes care tasks and potentially compromise health status. Therefore, psychological symptoms, both clinical and subclinical, must be addressed. In addition to impacting a person's ability to carry out self-management and the association of behavioral health diagnoses with poorer short-term glycemic stability, symptoms of emotional distress are associated with increased mortality risk (386,393).

There are opportunities for diabetes health care professionals to routinely monitor and screen psychosocial status in a timely and efficient manner for referral to appropriate services (394,395). Various health care professionals working with people with diabetes may contribute to psychosocial care in different ways based on training, experience, need, and availability (380,396,397). Ideally, qualified behavioral health professionals with specialized training and experience in diabetes should be integrated with or provide collaborative care as part of diabetes care teams (398–401). Referrals for in-depth assessment and treatment for psychosocial concerns should be made to such behavioral health professionals when indicated (381,402,403). A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C and behavioral health outcomes (404). There was a limited association between the effects on A1C and behavioral health, and no intervention characteristics predicted benefit on both outcomes. However, cost analyses have shown that behavioral health interventions are both effective and cost-efficient approaches to the prevention of diabetes (405).

Screening

Health care teams should develop and implement psychosocial screening protocols to ensure routine monitoring of psychosocial well-being and to identify potential concerns among people with diabetes, following published guidance and recommendations (406–411). Topics to screen for may include, but are not limited to, attitudes about diabetes, expectations for treatment and outcomes (especially related to starting a new treatment or technology), general and diabetes-related mood, stress, and/or quality of life (e.g., diabetes distress, depressive symptoms, anxiety symptoms, and/or fear of hypoglycemia), available resources (financial, social, family, and emotional), and/or psychiatric history. Given elevated rates of suicidality among people with diabetes (412–415), screening for suicidality may also be appropriate (416–418), similar to U.S. Preventive Services Task Force statements regarding screening for some adolescents and adults in the general population (419,420). A list of age-appropriate screening and evaluation measures is provided in the ADA position statement "Psychosocial Care for People with Diabetes" (1), and guidance has been published about selection of screening tools, clinical thresholds, and frequency of screening (408,421). Key opportunities for psychosocial screening occur at diabetes diagnosis, during regularly scheduled management visits, during hospitalizations, with new onset of complications, during significant transitions in care such as from pediatric to adult care teams (422), at the time of medical treatment changes, or when problems with achieving A1C goals, quality of life, or self-management are identified. People with diabetes are likely to exhibit psychological vulnerability at diagnosis, when their medical status changes (e.g., end of the honeymoon period), when the need for intensified treatment is evident, and when complications are discovered. Significant changes in life circumstances and SDOH are known to considerably affect a person's ability to self-manage their condition. Thus, screening for SDOH (e.g., loss of employment, birth of a child, or other family-based stresses) should also be incorporated into routine care (423). In cir-cumstances where individuals other than the person with diabetes are significantly involved in diabetes management (e.g., caregivers or family members), these issues should be monitored and treated by appropriate professionals (422,424,425).

Standardized, validated, age-appropriate tools for psychosocial monitoring and screening can also be used (1). The ADA provides access to tools for screening specific psychosocial topics, such as diabetes distress, fear of hypoglycemia, and other relevant psychological symptoms at professional.diabetes.org/sites/default/files/media/ada_mental_health_toolkit_questionnaires.pdf. Additional information about developmentally specific psychosocial screening topics is available in Section 14, "Children and Adolescents," and Section 13, "Older Adults." Health care professionals may also use informal verbal inquires, for example, by asking whether there have been persistent changes in mood during the past 2 weeks or since the individual's last appointment and whether the person can identify a triggering event or change in circumstances. Diabetes care professionals should also ask whether there are new or different barriers to treatment and self-management, such as feeling overwhelmed or stressed by having diabetes (see DIABETES DISTRESS, below), changes in finances, or competing medical demands (e.g., the diagnosis of a comorbid condition).

Psychological Assessment and Treatment

When psychosocial concerns are identified, referral to a qualified behavioral health professional, ideally one specializing in diabetes, should be made for comprehensive evaluation, diagnosis, and treatment (380,381,402,403). Indications for referral may include positive screening for overall stress related to work-life balance, diabetes distress, diabetes management difficulties, depression, anxiety, disordered eating, and cognitive dysfunction (see **Table 5.2** for a complete list). It is preferable to incorporate psychosocial assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status to occur (39,391). Health care professionals should identify behavioral health professionals, knowledgeable about diabetes treatment and the psychosocial aspects of diabetes, to whom they can refer individuals. The ADA provides a list of behavioral health professionals who have specialized expertise or who have received education about psychosocial and behavioral issues related to diabetes in the ADA Mental Health Professional Directory (professional.diabetes.org/ada-mental-health-provider-directory). Ideally, behavioral health professionals should be embedded in diabetes care settings. In recognition of limited behavioral health resources and to optimize availability, other health care professionals who have been trained in behavioral health interventions may also provide this specialized psychosocial care (396,399,426,427). Although some health care professionals may not feel qualified to treat psychological problems (428), strengthening the relationship between a person with diabetes and the health care professional may increase the likelihood of the individual accepting referral for other services. Collaborative care interventions and a team approach have demonstrated efficacy in diabetes self-management, outcomes of depression, and psychosocial functioning (5,6). The ADA provides resources for a range of health professionals to support behavioral health in people with diabetes at professional.diabetes.org/meetings/behavioral-health-toolkit.

Evidence supports interventions for people with diabetes and psychosocial concerns, including issues that affect behavioral health. Successful therapeutic approaches include cognitive behavioral (400,402,429,430) and mindfulness-based therapies (427,431,432). See the sections below for details about interventions for specific psychological concerns. Behavioral interventions may also be indicated in a preventive manner even in the absence of positive psychosocial screeners, such as resilience-promoting interventions to prevent diabetes distress in adolescence (433,434) and behavioral family interventions to promote collaborative family diabetes management in early adolescence (435,436) or to support adjustment to a new treatment plan or technology (65). Psychosocial interventions can be delivered via digital health platforms (437). Group-based or shared diabetes appointments that address both medical and psychosocial issues relevant to living with diabetes are a promising model to consider (397,438).

Although efficacy has been demonstrated with psychosocial interventions, there has been varying success regarding sustained increases in engagement in health behaviors and improved glycemic outcomes associated with behavioral health issues. Thus, health care professionals should systematically monitor these outcomes following implementation of current evidence-based psychosocial treatments to determine ongoing needs.

Diabetes Distress

Recommendation

5.39 Screen people with diabetes, caregivers, and family members for diabetes distress at least annually, and consider more frequent monitoring when treatment targets are not met, at transitional times, and/or in the presence of diabetes complications. Health care professionals can address diabetes distress and may consider referral to a qualified behavioral health professional, ideally one with experience in diabetes, for further assessment and treatment if indicated. **B**

Diabetes distress is very common (391, 439–441). While it shares some features with depression, diabetes distress is distinct and has unique relationships with glycemic and other outcomes (440,442). Diabetes distress refers to significant negative psychological reactions related to emotional burdens and worries specific to an individual's experience in having to manage a severe, complicated, and demanding chronic condition such as diabetes (439,440,443). The constant behavioral demands of diabetes self-management (medication dosing, frequency, and titration as well as monitoring of glucose, food intake, eating patterns, and physical activity) and the potential or actuality of disease progression are directly associated with reports of diabetes distress (439). The prevalence of diabetes distress is reported to be 18–45%, with an incidence of 38–48% over 18 months in people with type 2 diabetes (443). In the second Diabetes Attitudes, Wishes, and Needs (DAWN2) study, significant diabetes distress was reported by 45% of the participants, but only 24% reported that their health care teams asked them how diabetes affected their lives (391). Similar rates have been identified among adolescents with type 1 diabetes (441) and in parents of youth with type 1 diabetes. High levels of diabetes distress significantly impact medication-taking behaviors and are linked to higher A1C, lower self-efficacy, and less optimal

Table 5.2—Situations that warrant referral of a person with diabetes to a qualified behavioral health professional for evaluation and treatment

- A positive screen on a validated screening tool for depressive symptoms, diabetes distress, anxiety, fear of hypoglycemia, suicidality, or cognitive impairment
- The presence of symptoms or suspicions of disordered eating behavior, an eating disorder, or disrupted patterns of eating
- Intentional omission of insulin or oral medication to cause weight loss is identified
- A serious mental illness is suspected
- In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, failure to achieve expected developmental milestones, or significant distress
- Low engagement in diabetes self-management behaviors, including declining or impaired ability to perform diabetes self-management behaviors
- Before undergoing bariatric or metabolic surgery and after surgery, if assessment reveals an ongoing need for adjustment support

eating and exercise behaviors (5,439,443). Diabetes distress is also associated with symptoms of anxiety, depression, and reduced health-related quality of life (444).

Diabetes distress should be routinely monitored (445) using diabetes-specific validated measures (1), such as those available through the ADA's website (professional.diabetes.org/sites/default/files/media/ada_mental_health_toolkit_questionnaires.pdf). As there are diabetes distress measures that are validated for people with type 1 and type 2 diabetes at different life stages, it is important to select a tool that is appropriate for each person or population. If diabetes distress is identified, it should be acknowledged and addressed. If indicated, the person should be referred for follow-up care (403). This may include specific diabetes education to address areas of diabetes self-care causing distress and impacting clinical management and/or behavioral intervention from a qualified behavioral health professional, ideally one with expertise in diabetes, or from another trained health care professional. Several educational and behavioral intervention strategies have demonstrated benefits for diabetes distress and, to a lesser degree, glycemic outcomes, including education, psychological therapies, such as cognitive behavioral therapy (CBT) and mindfulness-based therapies, and health behavior change approaches, such as motivational interviewing (429,430,446,447). Data support diabetes distress interventions delivered using technology to reduce diabetes distress (437), including phone-delivered CBT combined with a smartphone application for CBT (448). DSMES has been shown to reduce diabetes distress (5) and may also benefit A1C when combined with peer support (449). It may be helpful to provide counseling regarding expected diabetes-related versus generalized psychological distress, both at diagnosis and when disease state or treatment changes occur (450). A multisite RCT with adults with type 1 diabetes and elevated diabetes distress and A1C demonstrated large improvements in diabetes distress and small reductions in A1C through two 3-month intervention approaches: a diabetes education intervention with goal setting and a psychological intervention that included emotion regulation skills, motivational interviewing, and goal setting (451). Among adults with type 2 diabetes in the Veterans Affairs system, an RCT demonstrated benefits of integrating a single session of mindfulness intervention into DSMES, followed by a booster session and mobile app-based home practice over 24 weeks, with the strongest effects on diabetes distress (452). An RCT of CBT demonstrated positive benefits for diabetes distress, A1C, and depressive symptoms for up to 1 year among adults with type 2 diabetes and elevated symptoms of distress or depression (453). An RCT among people with type 1 and type 2 diabetes found mindful self-compassion training increased self-compassion, reduced depression and diabetes distress, and improved A1C (454). An RCT of a resilience-focused cognitive behavioral and social problem-solving intervention compared with diabetes education (434) in teens with type 1 diabetes showed that diabetes distress and depressive symptoms were significantly reduced for up to 3 years post-intervention, although neither A1C nor self-management behaviors improved over time. These recent studies support that a combination of educational, behavioral, and psychological intervention approaches is needed to address distress, depression, and A1C.

As with treatment of other diabetes-associated behavioral and psychosocial factors affecting disease outcomes, there are few outcome data on long-term systematic treatment of diabetes distress integrated into routine care. As the diabetes disease course and its management are fluid, it can be expected that related distress may fluctuate and may need different methods of remediation at different points in the life course and as disease progression occurs.

Anxiety

Recommendation

5.40 Consider screening people with diabetes for anxiety symptoms, fear of hypoglycemia, or diabetes-related worries. Health care professionals can discuss diabetes-related worries and should consider referral to a qualified behavioral health professional for further assessment and treatment if anxiety symptoms indicate interference with diabetes self-management behaviors or quality of life. **B**

Anxiety symptoms and diagnosable disorders (e.g., generalized anxiety disorder, body dysmorphic disorder, obsessive compulsive disorder, specific phobias, and posttraumatic stress disorder) are common in people with diabetes (455). The Behavioral Risk Factor Surveillance System estimated the lifetime prevalence of generalized anxiety disorder to be 19.5% in people with either type 1 or type 2 diabetes (456). A common diabetes-specific concern is fear related to hypoglycemia (457–459), which may explain avoidance of behaviors associated with lowering glucose, such as increasing insulin doses or frequency of monitoring. Factors related to greater fear of hypoglycemia in people with diabetes and family members include history of nocturnal hypoglycemia, presence of other psychological concerns, and sleep concerns (460). See Section 6, "Glycemic Goals and Hypoglycemia," for more information about impaired awareness of hypoglycemia and related fear of hypoglycemia. Other common sources of diabetes-related anxiety include not meeting blood glucose targets (455), insulin injections or infusion (461), and onset of complications (1). People with diabetes who exhibit excessive diabetes self-management behaviors well beyond what is prescribed or needed to achieve glycemic goals may be experiencing symptoms of obsessive-compulsive disorder (462). General anxiety is a predictor of injection-related anxiety and is associated with fear of hypoglycemia (458,463).

Psychological and behavioral care can be helpful to address symptoms of anxiety in people with diabetes. Among adults with type 2 diabetes and elevated depressive symptoms, an RCT of collaborative care demonstrated benefits on anxiety symptoms for up to 1 year (464). An RCT of CBT for adults with type 2 diabetes showed a reduction in health anxiety, with CBT accounting for 77% of the reduction in health anxiety at 16 weeks of follow-up; this trial also found decreased depressive symptoms and diabetes distress (465). Additionally, an RCT showed switching from intermittently scanned CGM without alerts to real-time CGM with alert functionality in adults with type 1 diabetes decreased hypoglycemia-related anxiety at 24 months of follow-up while reducing A1C (466). Thus, specialized behavioral intervention from a qualified professional is needed to treat hypoglycemia-related anxiety.

Depression

Recommendations

5.41 Conduct at least annual screening of depressive symptoms in all people with diabetes and more frequently among those with a self-reported history of depression. Use age-appropriate, validated depression screening measures, recognizing that further evaluation will be necessary for individuals who have a positive screen. **B**

5.42 Beginning at diagnosis of complications or when there are significant changes in medical status, consider assessment for depression. **B**

5.43 Refer to qualified behavioral health professionals or other trained health care professionals with experience using evidence-based treatment approaches for depression in conjunction with collaborative care with the diabetes treatment team. **A**

History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes, especially if the individual has other risk factors, such as obesity and family history of type 2 diabetes (467–469). Elevated depressive symptoms and depressive disorders are common among people with diabetes (385,459), affecting approximately one in four people with type 1 or type 2 diabetes (390), and among parents of youth with diabetes (470). Thus, routine screening for depressive symptoms is indicated in this high-risk population, including people with type 1 or type 2 diabetes, gestational diabetes mellitus, and postpartum diabetes. Regardless of diabetes type, women have significantly higher rates of depression than men (471).

Routine monitoring with age-appropriate validated measures (1) can help to identify if referral is warranted (403,410). Multisite studies have demonstrated feasibility of implementing depressive symptom screening protocols in diabetes clinics and published practical guides for implementation (407–410,472). Adults with a history of depressive symptoms need ongoing monitoring of depression recurrence within the context of routine care (467). Integrating behavioral and physical health care can improve outcomes. When a person with diabetes is receiving psychological therapy, the behavioral health professional should be incorporated into or collaborate with the diabetes treatment team (473). As with DSMES, person-centered collaborative care approaches have been shown to improve both depression and medical outcomes (473). Depressive symptoms may also be a manifestation of reduced quality of life secondary to disease burden (also see DIABETES DISTRESS, above) and resultant changes in resource allocation impacting the person and their family. When depressive symptoms are identified, it is important to query origins, both diabetes-specific ones and those due to other life circumstances (444,474).

Trials have shown consistent evidence of improvements in depressive symptoms and variable benefits for A1C when depression is simultaneously treated (401,473, 475), whether through pharmacological treatment, group therapy, psychotherapy, or collaborative care (398,429,430,476, 477). Psychological interventions targeting depressive symptoms have shown efficacy when delivered via digital technologies (478). A systematic review of internet-delivered CBT studies indicated benefits across chronic health conditions, including diabetes (479). For people with diabetes, an RCT comparing internet plus telephonic CBT to usual care found moderate to large improvements in depressive symptoms at 12 months (480). Physical activity interventions also demonstrate benefits for depressive symptoms and A1C (318). It is important to note that the medical treatment plan should also be monitored in response to reduction in depressive symptoms.

Disordered Eating Behavior

Recommendations

5.44 Consider screening for disordered or disrupted eating using validated screening measures when hyperglycemia and weight loss are unexplained based on self-reported behaviors related to medication dosing, meal plan, and physical activity. In addition, a review of the medical treatment plan is recommended to identify potential treatment-related effects on hunger/caloric intake. **B**

5.45 Consider reevaluating the treatment plan of people with diabetes who present with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating, in consultation with a qualified professional. Key qualifications include familiarity with diabetes disease physiology, treatments for diabetes and disordered eating behaviors, and weight-related and psychological risk factors for disordered eating behaviors. **B**

Estimated prevalence of disordered eating behavior and diagnosable eating disorders in people with diabetes varies (481–483). For people with type 1 diabetes, insulin omission causing glycosuria in order to lose weight is the most commonly reported disordered eating behavior (484,485); in people with type 2 diabetes, bingeing (excessive food intake with an accompanying sense of loss of control) is most commonly reported. For people with type 2 diabetes treated with insulin, intentional omission is also frequently reported (486). People with diabetes and diagnosable eating disorders have high rates of comorbid psychiatric disorders (487). People with type 1 diabetes and eating disorders often have high rates of diabetes distress and fear of hypoglycemia (488).

Diabetes care professionals should monitor for disordered eating behaviors using validated measures (489). When evaluating symptoms of disordered or disrupted eating (when the individual exhibits eating behaviors that appear maladaptive but are not volitional, such as bingeing caused by loss of satiety cues), etiology and motivation for the behavior should be evaluated (483,490). Mixed intervention results point to the need for treatment of eating disorders and disordered eating behavior in the context of the disease and its treatment. Given the complexities of treating disordered eating behaviors and disrupted eating patterns in people with diabetes, it is recommended that interprofessional care teams include or collaborate with a health professional trained to identify and treat eating behaviors with expertise in disordered eating and diabetes (491). Key qualifications for such professionals include familiarity with diabetes disease physiology, weight-related and psychological risk factors for disordered eating behaviors, and treatments for diabetes and disordered eating behaviors. More rigorous methods to identify underlying mechanisms of action that drive change in eating and treatment behaviors, as well as associated mental distress, are needed (492). Health care teams may consider the appropriateness of technology use among people with diabetes and disordered eating behaviors, although more research on the risks and benefits is needed (493). Caution should be taken in labeling individuals with diabetes as having a diagnosable psychiatric disorder, i.e., an eating disorder, when disordered or disrupted eating patterns are found to be associated with the disease and its treatment. In other words, patterns of maladaptive food intake that appear to have a psychological origin may be driven by physiologic disruption in hunger and satiety cues, metabolic perturbations, and/or secondary distress because of the individual's inability to control their hunger and satiety (483,490).

The use of incretin therapies may have potential relevance to the treatment of disrupted or disordered eating (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"). Incretin therapies work in the appetite and reward circuitries to modulate food intake and energy balance, reducing uncontrollable hunger, overeating, and bulimic symptoms (494), although mechanisms are not completely understood (495). Weight loss from these medications (496) may also improve quality of life. More research is needed about whether use of incretins and other medications affects physiologically based eating behavior in people with diabetes.

Serious Mental Illness

Recommendations

5.46 Provide an increased level of support for people with diabetes and serious mental illness through enhanced monitoring of and assistance with diabetes self-management behaviors. **B**

5.47 Monitor changes in body weight, glycemia, and lipids in adolescents and adults with diabetes who are prescribed second-generation antipsychotic medications; adjust the treatment plan accordingly, if needed. **C**

Studies of individuals with serious mental illness, particularly schizophrenia and other thought disorders, show significantly increased rates of type 2 diabetes (497). People with schizophrenia and other thought disorders who are prescribed antipsychotics should be monitored for prediabetes and type 2 diabetes because of the known comorbidity. Changes in body weight, glycemia, and lipids should be monitored every 12–16 weeks, unless clinically indicated sooner (498). Disordered thinking and judgment can be expected to make it difficult to engage in behavior that reduces risk factors for type 2 diabetes, such as restrained eating for weight management. Further, people with serious behavioral health disorders and diabetes frequently experience moderate psychological distress, suggesting pervasive intrusion of behavioral health issues into daily functioning (499). Serious mental illness is often associated with the inability to evaluate and apply information to make judgments about treatment options. When a person has an established diagnosis of a mental illness that impacts judgment, activities of daily living, and ability to establish a collaborative relationship with care professionals, it is helpful to include a nonmedical caretaker in decision-making regarding the medical treatment plan. This caretaker can help improve the person's ability to follow the agreed-upon treatment plan through both monitoring and caretaking functions (500).

Coordinated management of prediabetes or diabetes and serious mental illness is recommended to achieve diabetes treatment targets. The diabetes care team, in collaboration with other care professionals, should work to provide an enhanced level of care and self-management support for people with diabetes and serious mental illness based on individual capacity and needs. Such care may include remote monitoring, facilitating health care aides, and providing diabetes training for family members, community support personnel, and other caregivers. Qualitative research suggests that educational and behavioral intervention may provide benefit via group support, accountability, and assistance with applying diabetes knowledge (501).

Cognitive Capacity/Impairment

Recommendations

5.48 Cognitive capacity should be monitored throughout the life span for all individuals with diabetes, particularly in those who have documented cognitive disabilities, those who experience severe hypoglycemia, very young children, and older adults. **B**

5.49 If cognitive capacity changes or appears to be suboptimal for decision-making and/or behavioral self-management, referral for a formal assessment should be considered. **E**

Cognitive capacity is generally defined as attention, memory, logic and reasoning, and auditory and visual processing, all of which are involved in diabetes self-management behavior (502). Having diabetes (type 1 or type 2) over decades has been shown to be associated with cognitive decline (503–505). A host of factors have been linked with cognitive impairment in people with type 1 diabetes, including diabetes-specific (e.g., younger age at diagnosis, longer disease duration, more time in glycemic extremes, recurrent diabetic ketoacidosis, higher A1C, and presence of microvascular complications), other medical (e.g., dyslipidemia, intestinal flora, and poorer sleep quality), and sociodemographic (e.g., female gender and lower educational level) factors (506). Declines have been shown to impact executive function and information processing speed; they are not consistent between people, and evidence is lacking regarding a known course of decline (507). Diagnosis of dementia is more prevalent among people with diabetes, both type 1 and type 2 (508). Executive functioning is an aspect of cognitive capacity that has particular relevance to diabetes management. Attention deficit hyperactivity disorder has been linked with twice the risk of type 2 diabetes (509). Among youth and young adults with type 1 diabetes, lower executive functioning has been linked with more difficulties with diabetes self-management and higher A1C (510). In contrast, higher self-regulation has been linked with better emotional and diabetes-specific functioning (511). Thus, monitoring of cognitive capacity and skills among individuals with or at risk for diabetes is recommended, particularly regarding their ability to self-monitor and make judgments about their symptoms, physical status, and needed alterations to their self-management behaviors, all of which are mediated by executive function (508).

As with other disorders affecting mental capacity (e.g., major psychiatric disorders), the key issue is whether the person can collaborate with the care team to achieve optimal metabolic outcomes and prevent complications, both short and long term (499). When this ability is shown to be altered, declining, or absent, a lay care professional should be introduced into the care team who serves in the capacities of a day-to-day monitor as well as a liaison with the rest of the care team (1). Cognitive capacity also contributes to ability to benefit from diabetes education and may indicate the need for alternative teaching approaches as well as remote monitoring. Youth will need second-party monitoring (e.g., parents and adult caregivers) until they are developmentally able to evaluate necessary information for self-management decisions and to inform resultant behavior changes.

Episodes of severe hypoglycemia are independently associated with decline as well as the more immediate symptoms of mental confusion (512). Early-onset type 1 diabetes has been shown to be associated with potential long-term deficits in intellectual abilities, especially in the context of repeated episodes of severe hypoglycemia (513), and is correlated with higher A1C and sensor glucose values (514). (See Section 14, "Children and Adolescents," for information on early-onset diabetes and cognitive abilities and the effects of severe hypoglycemia on children's cognitive and academic performance.) Thus, for myriad reasons, cognitive capacity should be assessed during routine care to ascertain the person's ability to maintain and adjust self-management behaviors, such as dosing of medications, remediation approaches to glycemic excursions, etc., and to determine whether to enlist a caregiver in monitoring and decision-making regarding management behaviors. If cognitive capacity to carry out self-maintenance behaviors is questioned, an age-appropriate test of cognitive capacity is recommended (1). Cognitive capacity should be evaluated in the context of the person's age, for example, in very young children who are not expected to manage their disease independently and in older adults who may need active monitoring of treatment plan behaviors.

Cognitive decline is more severe in older adults with type 2 diabetes (515). Longitudinal epidemiological studies have documented that chronic hyperglycemia, older age, less education, retinopathy, and nephropathy are associated with diabetes-related cognitive dysfunction (516). Importantly, the risk of cognitive decline can be reduced through improved A1C (517). Exercise may be a potential nonpharmacological treatment pathway for cognitive impairment in older adults with type 2 diabetes (518,519).

Sleep Health

Recommendations

5.50 Consider screening for sleep health in people with diabetes, including symptoms of sleep disorders, disruptions to sleep due to diabetes symptoms or management needs, and worries about sleep. Refer to sleep medicine specialists and/or qualified behavioral health professionals as indicated. **B**

5.51 Counsel people with diabetes to practice sleep-promoting routines and habits (e.g., maintaining consistent sleep schedule and limiting caffeine in the afternoon). **A**

The associations between sleep problems and diabetes are complex: sleep disorders are a risk factor for developing type 2 diabetes (520,521) and possibly gestational diabetes mellitus (522,523). People with diabetes across the life span often experience sleep disruptions and reduced sleep quality (524,525), and sleep problems are also common in parents of youth with diabetes, especially soon after diagnosis (526,527). Disrupted sleep and sleep disorders, including obstructive sleep apnea (528), insomnia, and sleep disturbances (529), are common among people with diabetes. In type 1 diabetes, estimates of poor sleep range from 30% to 50% (530), and estimates of moderate to severe obstructive sleep apnea are >50% (531). In type 2 diabetes, 24–86% of people are estimated to have obstructive sleep apnea (532), 39% to have insomnia, and 8–45% to have restless leg syndrome (i.e., an uncontrollable urge to move legs) (533). Further, people with type 2 diabetes and restless leg syndrome are more likely to experience microvascular and macrovascular complications (534) as well as depression (535). Additionally, people with diabetes who perform shift work increase their risk for circadian rhythm disorders, which are associated with higher A1C (536), neuropathy (537), and decreased psychological well-being (537). Health care professionals should consider a comprehensive evaluation of the daily lifestyles of people with diabetes to decrease risk factors, including low sleep duration, shift work, and days off, given their associations with hyperglycemia, hypertension, dyslipidemia, and weight gain (538).

Sleep disturbances are associated with less engagement in diabetes self-management and may interfere with glucose levels within the target range among people with type 1 and type 2 diabetes (525,529,531,533,539,540). Risk of hypoglycemia poses specific challenges for sleep in people with type 1 diabetes and may require targeted assessment and treatment approaches (541). People with type 1 diabetes and their family members also describe diabetes management needs interfering with sleep and experiencing worries about poor sleep (542). Both helpful and challenging aspects of diabetes technology use have been described in relation to sleep (542), with the greatest perceived benefits being related to automated insulin delivery systems (543–545). For these reasons, detection and treatment of sleep disorders should be considered a part of standardized care for people with type 1 and type 2 diabetes.

As for the general population, there are evidence-based strategies to improve sleep for people with diabetes. CBT shows benefits for sleep in people with diabetes (429), including CBT for insomnia, which demonstrates improvements in sleep outcomes and possible small improvements in A1C and fasting glucose (546). There is also evidence that sleep extension and pharmacological treatments for sleep can improve sleep outcomes and possibly insulin resistance (541,546). Lastly, sleep education, or sleep hygiene, improves sleep quality, reduces A1C, and decreases insulin resistance in adults with type 2 diabetes (547). Thus, diabetes care professionals are encouraged to counsel people with diabetes to use sleep-promoting routines and practices, such as establishing a regular bedtime and rise time, creating a dark, quiet area for sleep with temperature and humidity control, establishing a pre-sleep routine, putting electronic devices (except diabetes management devices) in silent/off mode, exercising during the day, avoiding daytime naps, limiting caffeine and nicotine in the evening, avoiding spicy foods at night, and avoiding alcohol before bedtime (548). For people with diabetes who have significant sleep difficulties, referral to sleep specialists to address the medical and behavioral aspects of sleep is recommended, ideally in collaboration with the diabetes care professional (**Fig. 5.1**).

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6. Glycemic Goals and Hypoglycemia: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S111–S125 | https://doi.org/10.2337/dc24-S006

*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

ASSESSMENT OF GLYCEMIC STATUS

Glycemic status is assessed by A1C measurement, blood glucose monitoring (BGM) by capillary (finger-stick) devices, and continuous glucose monitoring (CGM) using time in range (TIR) or mean CGM glucose. Clinical trials of interventions that lower A1C have demonstrated the benefits of improved glycemia. Glucose monitoring via CGM or BGM (discussed in detail in Section 7, "Diabetes Technology") is useful for diabetes self-management, can provide nuanced information on glucose responses to meals, physical activity, and medication changes, and may be particularly useful in individuals taking insulin. CGM serves an increasingly important role in optimizing the effectiveness and safety of treatment in many people with type 1 diabetes and in selected people with type 2 diabetes or other forms of diabetes (e.g., cystic fibrosis–related diabetes). Individuals on a variety of insulin treatment plans can benefit from CGM with improved glucose levels, decreased hypoglycemia, and enhanced self-efficacy (Section 7, "Diabetes Technology") (1).

Glycemic Assessment

Recommendations

6.1 Assess glycemic status by A1C and/or appropriate continuous glucose monitoring (CGM) metrics at least two times a year. Assess more frequently (e.g., every 3 months) for individuals not meeting treatment goals, with frequent or severe hypoglycemia or hyperglycemia, changing health status, or growth and development in youth. **E**

6.2 Assess glycemic status at least quarterly and as needed in individuals whose therapy has recently changed and/or who are not meeting glycemic goals. **E**

A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

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Glycemic Assessment by A1C

The A1C test is the primary tool for assessing glycemic status in both clinical practice and clinical trials, and it is strongly linked to diabetes complications (2–4). A1C reflects average glycemia over approximately 2–3 months. The performance of laboratory tests for A1C is generally excellent for National Glycohemoglobin Standardization Program (NGSP)–certified assays (ngsp.org). Thus, A1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether glycemic goals have been reached and maintained. Adults with type 1 diabetes or type 2 diabetes with stable glycemia within goal may do well with A1C testing or other glucose assessment only twice per year. Unstable or intensively managed individuals or people not at goal with treatment adjustments may require testing more frequently (every 3 months, with interim assessments as needed) (5). The use of point-of-care A1C testing may provide an opportunity for more timely treatment changes during encounters between individuals with diabetes and health care professionals.

The A1C test is an indirect measure of average glycemia. Factors that affect hemoglobin or red blood cell characteristics or turnover may affect A1C. For example, conditions that affect red blood cell turnover (hemolytic anemia and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy) can interfere with the accuracy of A1C (6). Some hemoglobin variants can interfere with some A1C assays; however, most assays in use in the U.S. are accurate in individuals who are heterozygous for the most common variants (7). A1C cannot be measured in individuals with sickle cell disease (HbSS) or other homozygous hemoglobin variants (e.g., HbEE), since these individuals lack HbA (8). In individuals with conditions that interfere with the interpretation of A1C, alternative approaches to monitoring glycemic status should be used, including self-monitoring of blood glucose, CGM, and/or the use of glycated serum protein assays (discussed below). A1C does not provide a measure of glycemic variability or hypoglycemia. For individuals prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic status is best evaluated by the combination of results from BGM or CGM and A1C. Discordant results between BGM/CGM and A1C can be the result of the conditions outlined above or glycemic variability, with BGM/CGM missing the extremes.

As discussed in Section 2, "Diagnosis and Classification of Diabetes," there is controversy regarding the clinical significance of racial differences in A1C (9–12). There is an emerging understanding of genetic determinants that may modify the association between A1C and glucose levels (13). However, race is not a good proxy for these genetic differences that are likely present in a small minority of individuals of all racial groups. Therefore, race should not be a consideration for how A1C is used clinically for glycemic monitoring. Limitations of laboratory tests and within-person variability in glucose and A1C underscore the importance of using multiple approaches to glycemic monitoring and further evaluation of discordant results in all racial or ethnic groups.

Serum Glycated Protein Assays as Alternatives to A1C

Fructosamine and glycated albumin are alternative measures of glycemia that are approved for clinical use for monitoring glycemic status in people with diabetes. Fructosamine reflects total glycated serum proteins (mostly albumin). Glycated albumin assays reflect the proportion of total albumin that is glycated. Due to the turnover rate of serum protein, fructosamine and glycated albumin reflect glycemia over the past 2–4 weeks, a shorter-term time frame than that of A1C. Fructosamine and glycated albumin are highly correlated in people with diabetes, and the performance of modern assays is typically excellent. Fructosamine and glycated albumin have been linked to long-term complications in epidemiologic cohort studies (14–18). However, there have been few clinical trials, and the evidence base supporting the use of these biomarkers to monitor glycemic status is much weaker than that for A1C. In people with diabetes who have conditions where the interpretation of A1C may be problematic or when A1C cannot be measured (e.g., homozygous hemoglobin variants), fructosamine or glycated albumin may be useful alternatives to monitor glycemic status (8).

Correlation Between A1C and Blood Glucose Monitoring and Continuous Glucose Monitoring

Table 6.1 provides rough equivalents of A1C and mean glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) study. The ADAG study assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes (19,20). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation (r = 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ∼2,700 readings per A1C measurement in the ADAG trial.

Glycemic Assessment by Blood Glucose Monitoring

For many people with diabetes, glucose monitoring, either using BGM by capillary (finger-stick) devices or CGM in addition to regular A1C testing, is key for achieving glycemic goals. Major clinical trials of insulin-treated individuals have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes

Table 6.1—Equivalent A1C levels and estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ∼2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (19,20). Adapted from Nathan et al. (19).

complications (21). BGM is thus an integral component of effective therapy for individuals taking insulin. In recent years, CGM has become a standard method for glucose monitoring for most people with type 1 diabetes. Both approaches to glucose monitoring allow people with diabetes to evaluate individual responses to therapy and assess whether glycemic goals are being safely achieved. The specific needs and goals of individuals with diabetes should dictate BGM frequency and timing. Please refer to Section 7, "Diabetes Technology," for a more complete discussion of the use of BGM and CGM.

Glycemic Assessment by Continuous Glucose Monitoring

Recommendations

6.3 Standardized, single-page glucose reports from CGM devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. **E**

6.4 Time in range (TIR) is associated with the risk of microvascular complications and can be used for assessment of glycemic status. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan (**Table 6.2**). **C**

CGM is particularly useful in people with diabetes who are at risk for hypoglycemia and is commonly used in people with type 1 diabetes (21). Use of CGM in type 2 diabetes (as well as in several other forms of diabetes) is growing, especially in people who are taking insulin. TIR is a useful metric of glycemic status. A 10- to 14-day CGM assessment of TIR, with CGM wear of 70% or higher, and other CGM metrics can be used to assess glycemic status and are useful in clinical management (22–26). TIR, especially mean CGM glucose, correlates with A1C (27–31). Time below range (<70 and <54 mg/dL [<3.9 and <3.0 mmol/L]) and time above range (>180 mg/dL [>10.0 mmol/L]) are useful parameters for insulin dose adjustments and reevaluation of the treatment plan.

The international consensus on CGM provides guidance on standardized CGM metrics (**Table 6.2**) and their clinical interpretation (32). To make these metrics actionable, standardized reports with visual summaries, such as the ambulatory glucose profile (**Fig. 6.1**), are recommended (32) and can help individuals with diabetes and health care professionals interpret the data to guide treatment decisions (27,30). BGM and CGM can be useful to guide medical nutrition therapy and physical activity, prevent hypoglycemia, and aid medication management. CGM metrics, including TIR (with time below range and time above range), can provide helpful insights to inform a personalized diabetes management plan. Remote access to glucose data is growing and may help improve diabetes management (33–35).

CGM systems have evolved rapidly in both accuracy and affordability. As such, many individuals with diabetes have these data available to assist with self-management and their health care professionals' assessment of glycemic status. Reports can be generated from CGM that will allow the health care professional and person with diabetes to view TIR, a calculated glucose management indicator, and assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a 2019 consensus report, a report formatted as shown in **Fig. 6.1** can be generated (32). Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ∼7% (25,28). Note the goals of therapy next to each metric in **Fig. 6.1** (e.g., low, <4%; very low, <1%) as values to guide changes in therapy.

GLYCEMIC GOALS

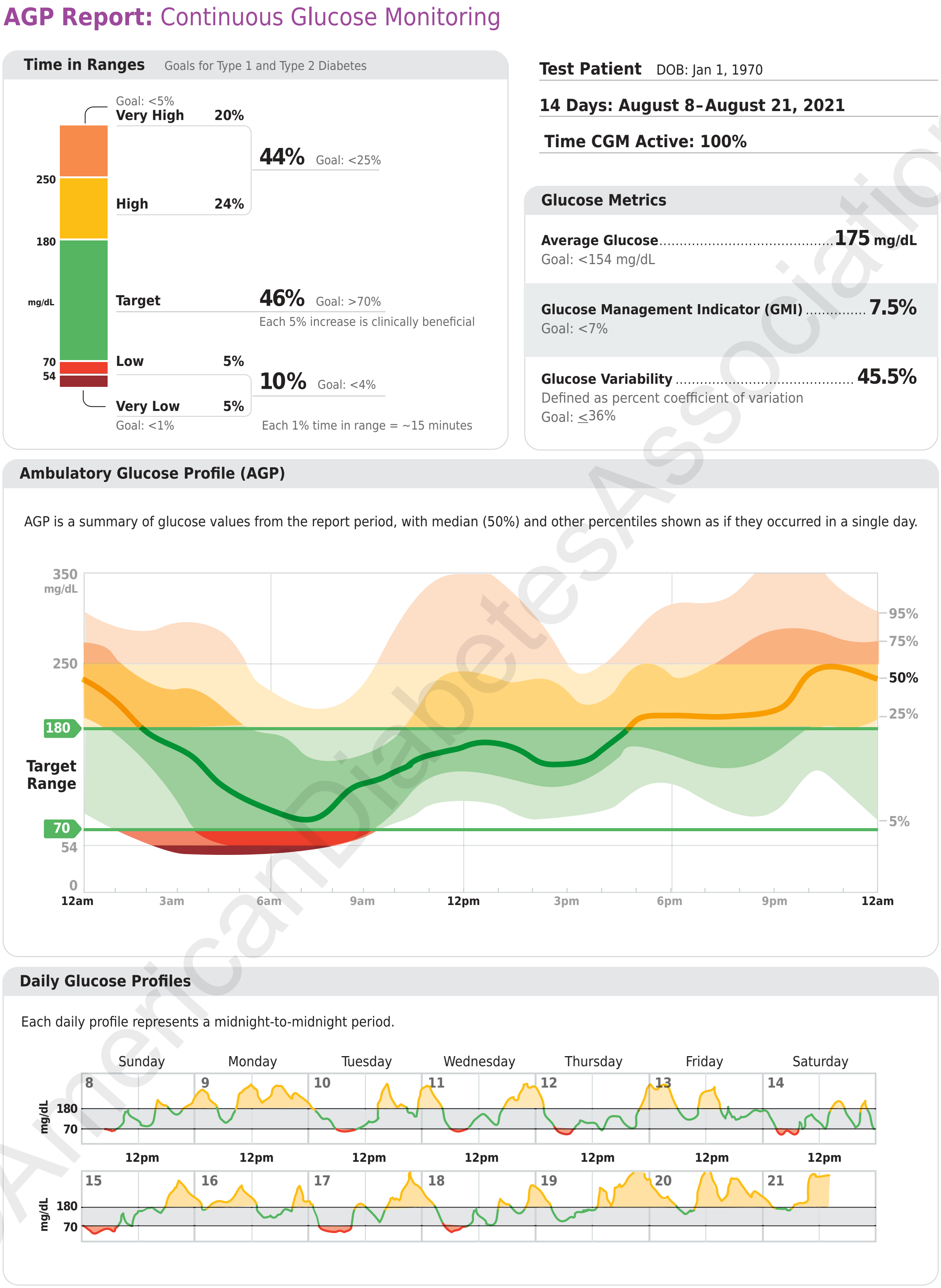
Recommendations

6.5a An A1C goal for many nonpregnant adults of <7% (<53 mmol/mol)

Table 6.2—Standardized CGM metrics for clinical care in nonpregnant individuals with type 1 or type 2 diabetes

Metric	Interpretation	Goals
1. Number of days CGM device is worn		14-day wear for pattern management
2. Percentage of time CGM device is active		70% of data from 14 days
3. Mean glucose	Simple average of glucose values	*
4. Glucose management indicator	Calculated value approximating A1C (not always equivalent)	*
5. Glycemic variability (%CV) target	Spread of glucose values	≤36%†
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia	<5% (most adults); <10% (older adults)
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia	<25% (most adults); <50% (older adults)‡
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range	>70% (most adults); >50% (older adults)
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia	<4% (most adults); <1% (older adults)§
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia	<1%

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Goals for these values are not standardized. †Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. ‡Goals are for level 1 and level 2 hyperglycemia combined. §Goals are for level 1 and level 2 hypoglycemia combined. Adapted from Battelino et al. (32).



AGP Report: Continuous Glucose Monitoring

Time in Ranges Goals for Type 1 and Type 2 Diabetes

Very High (Goal: <5%)	**20%**	**44%**	Goal: <25%
High	**24%**		
Target		**46%**	Goal: >70%
Low	**5%**	**10%**	Goal: <4%
Very Low (Goal: <1%)	**5%**		

Each 5% increase is clinically beneficial

Each 1% time in range = ~15 minutes

Test Patient DOB: Jan 1, 1970

14 Days: August 8–August 21, 2021

Time CGM Active: 100%

Glucose Metrics

Average Glucose .... **175** **mg/dL**
Goal: <154 mg/dL

Glucose Management Indicator (GMI) **7.5%**
Goal: <7%

Glucose Variability **45.5%**
Defined as percent coefficient of variation
Goal: ≤36%

Ambulatory Glucose Profile (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if they occurred in a single day.

350
mg/dL
250
180
Target Range
70
54
0
12am
3am
6am
9am
12pm
3pm
6pm
9pm
12am
95%
75%
50%
25%
5%

Daily Glucose Profiles

Each daily profile represents a midnight-to-midnight period.

Sunday
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
8
9
10
11
12
13
14
15
16
17
18
19
20
21
mg/dL
180
70
12pm

Figure 6.1—Key points included in a standard ambulatory glucose profile (AGP) report. Reprinted from Holt et al. (21).

without significant hypoglycemia is appropriate. **A**

6.5b If using an ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many nonpregnant adults is TIR >70% with time below range <4% and time <54 mg/dL (<3 mmol/L) <1%. For those with frailty or at high risk of hypoglycemia, a goal of >50% TIR with <1% time below range is recommended (**Fig. 6.1** and **Table 6.2**). **B**

6.6 On the basis of health care professional judgment and the preference of the person with diabetes, achievement of lower A1C levels than the goal of 7% (53 mmol/mol) may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **B**

6.7 Less stringent glycemic goals may be appropriate for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. **B**

6.8a Deintensify hypoglycemia-causing medications (insulin, sulfonylureas, or meglitinides), or switch to a medication class with lower hypoglycemia risk, for individuals who are at high risk for hypoglycemia, within individualized glycemic goals. **B**

6.8b Deintensify diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **B**

6.9 Reassess glycemic goals based on the individualized criteria shown in **Fig. 6.2**. **E**

6.10 Setting a glycemic goal during consultations is likely to improve patient outcomes. **E**

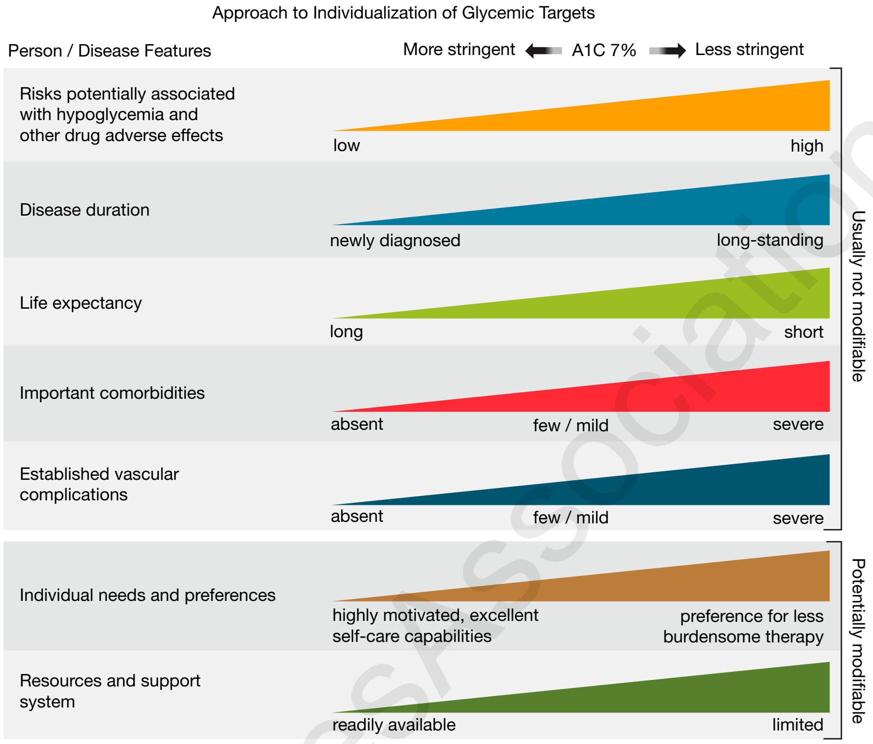

Approach to Individualization of Glycemic Targets
Person / Disease Features
More stringent
A1C 7%
Less stringent
Risks potentially associated with hypoglycemia and other drug adverse effects
low
high
Disease duration
newly diagnosed
long-standing
Life expectancy
long
short
Important comorbidities
absent
few / mild
severe
Established vascular complications
absent
few / mild
severe
Usually not modifiable
Individual needs and preferences
highly motivated, excellent self-care capabilities
preference for less burdensome therapy
Resources and support system
readily available
limited
Potentially modifiable

Figure 6.2—Person and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (36).

For all populations, it is critical that the glycemic goals be woven into the overall person-centered strategy (**Fig. 6.2**) (36). For example, less stringent A1C goals are appropriate for individuals with limited life expectancy and/or significant functional and cognitive impairments. In a very young child, safety and simplicity may outweigh the need for glycemic stability in the short run. Recommended glycemic goals for many nonpregnant adults are shown in **Table 6.3**. The recommendations include blood glucose levels that appear to correlate with an A1C of <7% (<53 mmol/mol). For glycemic goals in older adults, please refer to Section 13, "Older Adults." For glycemic goals in children, please refer to Section 14, "Children and Adolescents." For glycemic goals during pregnancy, please refer to Section 15, "Management of Diabetes in Pregnancy."

The health care professional needs to work with the individual (as well as with family members and caregivers) and should consider adjusting goals for simplifying the treatment plan if this change is needed to improve safety and medication-taking behavior. Setting specific glycemic (and other) goals during consultations is likely to improve outcomes for individuals with diabetes (37).

Glucose Lowering and Microvascular Complications

Hyperglycemia defines diabetes, and achieving glycemic goals is fundamental to diabetes management. The level of chronic hyperglycemia is the best-established concomitant risk factor associated with microvascular complications (i.e., diabetic retinopathy, nephropathy, and neuropathy). This is best understood by the fact that nerve, retinal, and kidney cells do not require insulin for intracellular glucose entry. Consequently, these cells, when exposed to elevated ambient glucose levels even in the presence of insulin deficiency (absolute or relative), will result in intracellular metabolic dysfunction and increased risk of microvascular complications.

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (<53 mmol/mol)*†
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose‡	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individuals. †CGM may be used to assess glycemic status as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (per **Fig. 6.2**). ‡Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

The Diabetes Control and Complications Trial (DCCT) (38), a prospective randomized controlled trial of intensive (mean A1C ∼7% [53 mmol/mol]) versus standard (mean A1C ∼9% [75 mmol/mol]) glycemic control in people with type 1 diabetes, showed definitively that better glycemic status is associated with 50–76% reductions in rates of development and progression of microvascular complications (retinopathy, neuropathy, and diabetic kidney disease). Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (39,40) demonstrated persistence of these microvascular benefits over two decades even though the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (41) and UK Prospective Diabetes Study (UKPDS) (42,43) examined the effects of "intensive glycemic control" among people with short-duration type 2 diabetes, although glycemic lowering in these studies was not intensive by current standards (mean A1C was 7.1% vs. 9.4% in the Kumamoto Study and 7.0% vs. 7.9% in UKPDS). These trials found lower rates of microvascular complications in the intervention arms, with long-term follow-up of the UKPDS cohorts showing enduring effects on most microvascular complications (44). These studies highlight the long-term benefits of early glycemic lowering in type 2 diabetes.

Therefore, improved glycemia has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (2,45). The DCCT (38) and UKPDS (46) studies demonstrated a curvilinear relationship between A1C and microvascular complications. Such results suggest that, on a population level, the greatest number of complications will be averted by taking individuals with diabetes from very high to moderate glycemic levels. These analyses also suggest that further lowering of A1C from 7% to 6% (53 mmol/mol to 42 mmol/mol) is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. The implication of these findings is that there is no need to deintensify therapy for an individual with an A1C between 6% and 7% in the setting of low hypoglycemia risk with a long life expectancy. There are newer agents that do not cause hypoglycemia, making it possible to maintain glycemic status without the risk of hypoglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"). Moreover, CGM use was not as common when these trials were conducted and automated insulin delivery systems were not available, which have been shown to improve glucose levels without increasing hypoglycemia.

Among individuals with type 2 diabetes, three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes. The ADVANCE and VADT trials found modest reduction in nephropathy with intensive glycemic control; ACCORD was stopped after a median of 3.5 years due to higher mortality in the intervention arm (47–51). Importantly, these landmark studies were conducted prior to the approval of glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors, and intensive glycemic control was achieved predominantly through greater use of insulin. Findings from these studies, including the concerning increase in mortality in the intensive treatment arm of ACCORD, suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes using medications with a high risk for hypoglycemia.

Glucose Lowering and Cardiovascular Disease Outcomes

Cardiovascular disease (CVD) is a more common cause of death than microvascular complications in populations with diabetes. The modern multifaceted management of diabetes, with a focus on the treatment of hypertension and the use of statins, has reduced the prevalence of atherosclerotic CVD to around double compared with that of people without diabetes (52).

The DCCT in individuals with type 1 diabetes and the UKPDS, ACCORD, ADVANCE, and VADT studies in type 2 diabetes all attempted to address whether intensive glycemic control reduced CVD events (38,47, 48,50). ACCORD, ADVANCE, and VADT were conducted in relatively older participants with a longer duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. Details of these studies are reviewed extensively in the joint ADA position statement "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (53).

No significant reduction in composite CVD events was demonstrated at the end of the intervention in any of these studies, and ACCORD was stopped prematurely at 3.5 years because of an increase in total mortality, particularly sudden CVD deaths. Serious concerns with the intensive glycemic treatment plan used in ACCORD included the rapid escalation of therapies, the early use of large doses of insulin, massive weight gain, and frequent hypoglycemia. These overall negative results were not unexpected, as blood glucose has subsequently been shown to be a relatively weak CVD risk factor in isolation compared with other CVD risk factors, such as hypertension or hypercholesterolemia. Consequently, even if a wide separation in A1C could be safely obtained, it would take a long time for the CVD benefit to accrue. However, meta-analysis of individual participant data from UKPDS, ACCORD, ADVANCE, and VADT demonstrated a significant reduction in myocardial infarctions and major CVD events but no difference in stroke, heart failure, or mortality between intensive and less intensive glycemic control (54).

Longer-term epidemiological follow-up has been performed in these studies, and a clear pattern of CVD benefit has emerged (55–57). In the post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction, stroke, or cardiovascular death compared with those previously randomized to the standard arm (55). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (56) and to be associated with a modest reduction in all-cause mortality (58).

UKPDS post-trial monitoring, with 20 years of total follow-up, has shown reductions in myocardial infarctions and total mortality both in the group of overweight individuals treated with metformin and in the group previously treated intensively with sulfonylureas or insulin (44). Shorter overall follow-up of the VADT (10 years) has shown a significant reduction in the primary outcome of major CVD events, with myocardial infarctions and heart failure being the commonest outcomes (57). In contrast, shorter follow-up of the ADVANCE study in the Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation Post Trial Observational Study (ADVANCE-ON) demonstrated no significant effect on CVD events (59). Even in the epidemiological follow-up of ACCORD in the Action to Control Cardiovascular Risk in Diabetes Follow-On Study (ACCORDION), the excess increase in total mortality that was seen during 3.5 years of intensive treatment was reduced by returning to conventional control, so that there was no difference in total mortality after a total of 9 years of follow-up and the increase in CVD deaths was obtunded (60). Collectively, the results of these studies confirm that long-term intensive glycemic control reduces CVD events, particularly myocardial infarctions.

As discussed above, these landmark studies in individuals with type 2 diabetes need to be considered with the important caveat that GLP-1 receptor agonists and SGLT2 inhibitors were not yet in clinical use. These agents with established cardiovascular and renal benefits appear to be safe and beneficial in this group of individuals at high risk for cardiorenal complications. Randomized clinical trials examining these agents for cardiovascular safety were not designed to test higher versus lower A1C; therefore, beyond post hoc analysis of these trials, we do not have evidence that it is the glucose lowering per se by these agents that confers the CVD and renal benefit (61). Additional beneficial pleotropic effects of these agents may include weight loss, hemodynamic effects, blood pressure lowering, and anti-inflammatory changes.

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (62). Therefore, health care professionals should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in people in whom such targets cannot be safely and reasonably achieved. As discussed in Section 9, "Pharmacologic Approaches to Glycemic Treatment," addition of specific SGLT2 inhibitors or GLP-1 receptor agonists that have demonstrated CVD benefit is recommended in individuals with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (63):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or a GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C goal.

Setting and Modifying Glycemic Goals

Glycemic goals and management should be individualized and not one size fits all. To prevent both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to individualized goals (53,64).

Numerous factors must be considered when setting a glycemic goal. The ADA proposes general goals that are appropriate for many people but emphasizes the importance of individualization based on key patient characteristics. Glycemic goals must be individualized in the context of shared decision-making to address individual needs and preferences and consider characteristics that influence risks and benefits of therapy; this approach may optimize engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. This figure is not designed to be applied rigidly in the care of a given individual but to be used as a broad framework to guide clinical decision-making (36) and engage people with type 1 and type 2 diabetes in shared decision-making. More aggressive goals may be recommended if they can be achieved safely and with an acceptable burden of therapy and if life expectancy is sufficient to reap the benefits of stringent goals. Less stringent goals (e.g., A1C up to 8% [64 mmol/mol]) may be recommended if the individual's life expectancy is such that the benefits of an intensive goal may not be realized or if the risks and burdens outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment plans, including setting higher glycemic goals.

Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed individuals and/or those without comorbidities that limit life expectancy may benefit from intensive glycemic goals proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS suggested that there is metabolic memory, or a legacy effect, in which a finite period of intensive glucose lowering yielded benefits that extended for decades after that period ended. However, there are few recent data on the effects of long-term glucose lowering using modern treatment strategies. Thus, a finite period of intensive treatment to near-normal A1C may yield enduring benefits even if treatment is subsequently deintensified as characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive treatment. Also, with longer disease duration, diabetes may become more difficult to control, with increasing risks and burdens of therapy. Thus, glycemic goals should be reevaluated over time to balance the risks and benefits.

Accordingly, clinicians should continue to evaluate the balance of risks and benefits of diabetes medications for individuals who have achieved individualized glycemic goals, and they should deintensify (decrease the dose or stop) diabetes medications where their risks exceed their benefits. Hypoglycemia is the major risk to individuals treated with insulin, sulfonylureas, or meglitinides, and it is appropriate to deintensify these medications where there is a high risk for hypoglycemia (see HYPOGLYCEMIA RISK ASSESSMENT, below). Switching a high-hypoglycemia-risk medication to lower-hypoglycemia-risk therapy (see Section 9, "Pharmacologic Approaches to Glycemic Treatment") should be considered if needed to achieve individualized glycemic goals or where individuals have evidence-based indications for alternative medications (e.g., use of SGLT2 inhibitors in the setting of heart failure or diabetic kidney disease and use of GLP-1 receptor agonists in the setting of CVD or obesity). Clinicians should also consider medication burdens other than hypoglycemia, including tolerability, difficulties of administration, impact on education or employment, and financial cost. These factors should be balanced against benefits from glycemic lowering and disease-specific benefits of newer medications that may be independent of glycemic lowering (Section 9, "Pharmacologic Approaches to Glycemic Treatment"). Multiple trials have shown that deintensification of diabetes treatment can be achieved successfully and safely (65–68). It is important to partner with people with diabetes during the deintensification process to understand their goals of diabetes treatment and agree upon appropriate glycemic monitoring, glucose levels, and goals of care (69).

HYPOGLYCEMIA ASSESSMENT, PREVENTION, AND TREATMENT

Recommendations

6.11a History of hypoglycemia should be reviewed at every clinical encounter for all individuals at risk for hypoglycemia and evaluated as indicated. **C**

6.11b Clinicians should screen all individuals at risk for hypoglycemia for impaired hypoglycemia awareness. **E**

6.11c Clinicians should consider an individual's risk for hypoglycemia (see **Table 6.5**) when selecting diabetes medications and glycemic goals. **E**

6.11d Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia. **A**

6.12 Glucose is the preferred treatment for the conscious individual with glucose <70 mg/dL (<3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after initial treatment, repeat the treatment if hypoglycemia persists. **B**

6.13 Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not have to be reconstituted are preferred. **E**

6.14 All individuals taking insulin **A** or at risk for hypoglycemia **C** should receive structured education for hypoglycemia prevention and treatment, with ongoing education for those who experience hypoglycemic events.

6.15 One or more episodes of level 2 or 3 hypoglycemia should prompt reevaluation of the treatment plan, including deintensifying or switching diabetes medications if appropriate. **E**

6.16 Refer individuals with impaired hypoglycemia awareness to a trained health care professional to receive evidence-based intervention to help reestablish awareness of symptoms of hypoglycemia. **A**

6.17 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if impaired or declining cognition is found. **B**

Hypoglycemia Definitions and Event Rates

Hypoglycemia is often the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in **Table 6.4** (70). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (<3.9 mmol/L) but ≥ 54 mg/dL (≥ 3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes. Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, sweating, and hunger (71). Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience impaired hypoglycemia awareness, a measured glucose level <70 mg/dL (<3.9 mmol/L) is considered clinically important, regardless of symptoms. Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [<3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If an individual has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have impaired hypoglycemia awareness (discussed further in HYPOGLYCENMIA RISK ASSESSMENT, below). This clinical scenario warrants investigation and review of the treatment plan (72,73). Lastly, level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, irrespective of glucose level.

Hypoglycemia has a broad range of negative health consequences (74). Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Level 3 hypoglycemia was associated with mortality in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward (75). An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial and in clinical practice (76,77). Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury (78). Hypoglycemia may also cause substantial anxiety that can reduce the quality of life of individuals with diabetes and their caregivers and may contribute to problems with diabetes self-management and treatment (79–81). Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical treatment plan adjustment, behavioral intervention, delivery of diabetes

Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (<3.9 mmol/L) and ≥ 54 mg/dL (≥ 3.0 mmol/L)
Level 2	Glucose <54 mg/dL (<3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

Reprinted from Agiostratidou et al. (70).

Table 6.5—Assessment of hypoglycemia risk among individuals treated with insulin, sulfonylureas, or meglitinides

Clinical/biological risk factors	Social, cultural, and economic risk factors
Major risk factors • Recent (within the past 3–6 months) level 2 or 3 hypoglycemia • Intensive insulin therapy* • Impaired hypoglycemia awareness • End-stage kidney disease • Cognitive impairment or dementia	Major risk factors • Food insecurity • Low-income status§ • Homelessness • Fasting for religious or cultural reasons
Other risk factors • Multiple recent episodes of level 1 hypoglycemia • Basal insulin therapy* • Age ≥75 years† • Female sex • High glycemic variability‡ • Polypharmacy • Cardiovascular disease • Chronic kidney disease (eGFR <60 mL/min/1.73 m^2 or albuminuria) • Neuropathy • Retinopathy • Major depressive disorder	Other risk factors • Low health literacy • Alcohol or substance use disorder

Major risk factors are those that have a consistent, independent association with a high risk for level 2 or 3 hypoglycemia. Other risk factors are those with less consistent evidence or a weaker association. These risk factors are identified through observational analyses and are intended to be used for hypoglycemia risk stratification. Individuals considered at high risk for hypoglycemia are those with ≥1 major risk factor or who have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (87,88,92,94–97,113,146). Proximal causes of hypoglycemic events (e.g., exercise and sleep) are not included. eGFR, estimated glomerular filtration rate. *Rates of hypoglycemia are highest for individuals treated with intensive insulin therapy (including multiple daily injections of insulin, continuous subcutaneous insulin infusion, or automated insulin delivery systems), followed by basal insulin, followed by sulfonylureas or meglitinides. Combining treatment with insulin and sulfonylureas also increases hypoglycemia risk. †Accounting for treatment plan and diabetes subtype, the oldest individuals (aged ≥75 years) have the highest risk for hypoglycemia in type 2 diabetes; younger individuals with type 1 diabetes are also at very high risk. ‡Tight glycemic control in randomized trials increases hypoglycemia rates. In observational studies, both low and high A1C are associated with hypoglycemia in a J-shaped relationship. §Includes factors associated with low income, such as being underinsured or living in a socioeconomically deprived area.

self-management education and support, and use of technology to assist with hypoglycemia prevention and identification (73,82–85).

Studies of rates of hypoglycemia predominantly rely on claims data for hospitalizations and emergency department visits (86–89). These studies do not capture the level 1 and level 2 hypoglycemia that represent the vast majority of hypoglycemic events, and they also substantially underestimate level 3 hypoglycemia (86,90). Nevertheless, they reveal a substantial burden of hypoglycemia-related hospital utilization in the community (86–89). Level 1 and level 2 hypoglycemia can be ascertained from patient self-report (91) and are strong risk factors for subsequent level 3 hypoglycemia.

Hypoglycemia Risk Assessment

Assessment of an individual's risk for hypoglycemia includes evaluating clinical risk factors as well as relevant social, cultural, and economic factors (**Table 6.5**). Recommendations 6.11–6.17 group individuals with diabetes into two hypoglycemia risk categories with clinical significance. Individuals at risk for hypoglycemia are those treated with insulin, sulfonylureas, or meglitinides; clinically significant hypoglycemia is rare among individuals taking other diabetes medication classes (92,93). Individuals at high risk for hypoglycemia are the subset of individuals at risk for hypoglycemia who either have a major hypoglycemia risk factor or have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (**Table 6.5**). This risk stratification is based on epidemiologic studies of hypoglycemia risk (87,88,92,94–97). Validated tools have been developed to estimate hypoglycemia risk using predominantly electronic health record data (98–100). However, these tools do not include all of the important hypoglycemia risk factors, and more research is needed to determine how they can best be incorporated into clinical care.

Among individuals at risk for hypoglycemia, prior hypoglycemic events, especially level 2 or 3 events, are the strongest risk factors for hypoglycemia recurrence and severity (96,101–103). Hypoglycemia history should be assessed at every clinical encounter and should include hypoglycemic event frequency, severity, precipitants, symptoms (or lack thereof), and approach to treatment. It is essential to correlate home glucose readings, both from glucose meters and CGM systems, with symptoms and treatment, as individuals may experience and treat hypoglycemic symptoms without checking their glucose level (104), treat normal glucose values as hypoglycemic, or tolerate hypoglycemia without treatment either because of lack of symptoms or to avoid hyperglycemia.

Individuals at risk for hypoglycemia should also be screened for impaired hypoglycemia awareness (also called hypoglycemia unawareness or hypoglycemia-associated autonomic failure) at least yearly. Impaired hypoglycemia awareness is defined as not experiencing the typical counterregulatory hormone release at low glucose levels or the associated symptoms, which often occurs in individuals with long-standing diabetes or recurrent hypoglycemia (105). Individuals with impaired hypoglycemia awareness may experience confusion as the first sign of hypoglycemia, which can create fear of hypoglycemia and severely impact quality of life (106). Impaired hypoglycemia awareness dramatically increases the risk for level 3 hypoglycemia (107). The Clark and Gold scores are validated questionnaires to assess impaired hypoglycemia awareness (108,109). However, these questionnaires may be impractical for routine clinical use. A recommended strategy is to screen for impaired hypoglycemia awareness by asking individuals whether they ever have low blood glucose without feeling symptoms, or by asking at what blood glucose levels they typically begin to feel symptoms (and what those symptoms are), and follow up positive responses with a more detailed evaluation (105,110).

Other notable clinical and biological risk factors for hypoglycemia are older age, multimorbidity, cognitive impairment, chronic kidney disease and end-stage kidney disease in particular, CVD, depression, and neuropathy (92,93). Female sex has also been found to be an independent risk factor for hypoglycemia in multiple studies, although the mechanisms of this relationship are unclear and require further research (92). Cognitive impairment has a strong bidirectional association with hypoglycemia, and recurrent severe hypoglycemic episodes were associated with a greater decline in psychomotor and mental efficiency after long-term follow-up of the DCCT/EDIC cohort (111). Therefore, cognitive function should be routinely assessed among older adults with diabetes.

There are a number of important social, cultural, and economic hypoglycemia risk factors that should considered. Food insecurity is associated with increased risk of hypoglycemia-related emergency department visits and hospitalizations in low-income households, and this was shown to be mitigated by increased federal nutrition program benefits (112). In general, individuals with low annual household incomes (93), individuals who live in socioeconomically deprived areas (96), and individuals who are underinsured (97) or homeless (113) experience higher rates of emergency department visits and hospitalizations for hypoglycemia. Clinicians should also be aware of cultural practices that may influence glycemic management (which are discussed in detail in Section 5, “Facilitating Positive Health Behaviors”), such as fasting as part of religious observance. Fasting may increase the risk for hypoglycemia among individuals treated with insulin or insulin secretagogues if not properly planned for, so clinicians need to engage these individuals to codevelop a diabetes treatment plan that is safe and respectful of their traditions (114).

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (115,116), are noted as being particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glycemic goals, patient education, nutrition intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), physical activity management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve outcomes (105). CGM with automated low-glucose suspend and automated insulin delivery systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (117). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental (118,119).

Hypoglycemia Treatment

Health care professionals should counsel individuals with diabetes to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less (120–122). Individuals should be counseled to recheck their glucose 15 min after ingesting carbohydrates and to repeat carbohydrate ingestion and seek care for ongoing hypoglycemia. These instructions should be reviewed at each clinical visit.

For most individuals, 15 g carbohydrates should be ingested. Individuals using automated insulin delivery systems are recommended to ingest 5–10 g carbohydrates (except for hypoglycemia with exercise or with significant overestimation of carbohydrate/meal bolus) (123). The acute glycemic response to food correlates better with the glucose content than with the total carbohydrate content. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may slow and then prolong the acute glycemic response. Carbohydrate sources high in protein may increase insulin secretion and should not be used to treat hypoglycemia (124). Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. All individuals treated with insulin or who are at high risk of hypoglycemia as discussed above should be prescribed glucagon. For these individuals, clinicians should routinely review their access to glucagon, as appropriate glucagon prescribing is very low in current practice (125,126). An individual does not need to be a health care professional to safely administer glucagon. Those in close contact with, or having custodial care of, these individuals (family members, roommates, school personnel, childcare professionals, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. It is essential that they be explicitly educated to never administer insulin to individuals experiencing hypoglycemia. Glucagon was traditionally dispensed as a powder that requires reconstitution prior to injection. However, intranasal and ready-to-inject glucagon preparations are now widely available and are preferred due to their ease of administration resulting in more rapid correction of hypoglycemia (127–130). Although physical and chemical stability of glucagon is improved with newer formulations, care should be taken to replace glucagon products when they reach their expiration date and store glucagon based on specific product instructions to ensure safe and effective use. For currently available glucagon products and associated costs, see **Table 6.6**. Health insurance providers may prefer only select glucagon products, so it is important to check individuals’ insurance coverage and prescribe formulary products whenever possible.

Hypoglycemia Prevention

A multicomponent hypoglycemia prevention plan (**Table 6.7**) is critical to caring for individuals at risk for hypoglycemia. Hypoglycemia prevention begins by establishing an individual’s hypoglycemia history and risk factors, as discussed in HYPOGLYCEMIA RISK ASSESSMENT above. Structured patient education for hypoglycemia prevention and treatment is critical and has been shown to improve hypoglycemia outcomes (131,132). Education should ideally be provided through a diabetes self-management education and support program or by a trained diabetes educator, although these services are not available in many areas (133,134). If structured education is not available, clinicians should educate individuals at risk for hypoglycemia on hypoglycemia definitions, situations that may precipitate hypoglycemia (fasting, delayed meals, physical activity, and illness), blood glucose self-monitoring, avoidance of driving with hypoglycemia, step-by-step instructions on hypoglycemia treatment as discussed above, and glucagon use as appropriate (131).

Table 6.6—Median monthly (30-day) AWP and NADAC of glucagon formulations in the U.S.

Product	Form(s)	Median AWP* (min, max)	Median NADAC* (min, max)	Dosage(s)
Glucagon	Injection powder with diluent for reconstitution	$266 ($194, $369)	$249 ($225, $273)	1 mg
Glucagon	Nasal powder	$337	$270	3 mg
Glucagon	Prefilled pen, prefilled syringe	$368	$285	0.5 mg, 1 mg
Dasiglucagon	Prefilled pen, prefilled syringe	$371	NA	0.6 mg

AWP, average wholesale price; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP and NADAC prices are as of August 2023. *Calculated per unit (AWP [147] or NADAC [148]; median AWP or NADAC is listed alone when only one product and/or price is described).

CGM can be a valuable tool for detecting and preventing hypoglycemia in many individuals with diabetes, and it is recommended for insulin-treated individuals, especially those using multiple daily insulin injections or continuous subcutaneous insulin infusion. There is clinical trial evidence that CGM reduces rates of hypoglycemia in these populations. CGM can reveal asymptomatic hypoglycemia and help identify patterns and precipitants of hypoglycemic events (135,136). Real-time CGM can provide alarms that can warn individuals of falling glucose so that they can intervene (135,136). For more information on using BGM and CGM for hypoglycemia prevention, see Section 7, "Diabetes Technology."

An essential component of hypoglycemia prevention is appropriate modification to diabetes treatment in the setting of intercurrent illness (discussed in detail below) or to prevent recurrent hypoglycemic events. Level 2 or 3 hypoglycemic events especially should trigger a reevaluation of the individual's diabetes treatment plan, with consideration of deintensification of therapy within individualized glycemic goals.

Table 6.7—Components of hypoglycemia prevention for individuals at risk for hypoglycemia at initial, follow-up, and annual visits

Hypoglycemia prevention action	Initial visit	Every follow-up visit	Annual visit
Hypoglycemia history assessment	✓	✓	✓
Hypoglycemia awareness assessment	✓		✓
Cognitive function and other hypoglycemia risk factor assessment	✓		✓
Structured patient education for hypoglycemia prevention and treatment	✓	✓*	✓*
Consideration of continuous glucose monitoring needs	✓	✓	✓
Reevaluation of diabetes treatment plan with deintensification, simplification, or agent modification as appropriate	✓	✓†	✓†
Glucagon prescription and training for close contacts for insulin-treated individuals or those at high hypoglycemic risk	✓		✓
Training to reestablish awareness of hypoglycemia	✓‡		✓‡

The listed frequencies are the recommended minimum; actions for hypoglycemia prevention should be done more often as needed based on clinical judgment. *Indicated with recurrent hypoglycemic events or at initiation of medication with a high risk for hypoglycemia. †Indicated with any level 2 or 3 hypoglycemia, intercurrent illness, or initiating interacting medications. ‡Indicated when impaired hypoglycemia awareness is detected.

Individuals with impaired awareness of hypoglycemia benefit from, and should be referred to, training programs that can reestablish awareness of hypoglycemia. Fear of hypoglycemia and hypoglycemia unawareness often cooccur, so interventions aimed at treating one often benefit both (137). Formal, evidence-based training programs that have been developed include the Blood Glucose Awareness Training Program, Dose Adjusted for Normal Eating (DAFNE), and DAFNEplus (138–140). Where these programs are not available, training can be provided through qualified behavioral health professionals, diabetes educators, or other professionals with experience in this area, although this approach has not been evaluated in clinical trials. In addition, several weeks of avoidance of hypoglycemia can improve counterregulation and hypoglycemia awareness in many people with diabetes (141). Hence, individuals with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic goals (142).

INTERCURRENT ILLNESS

Stressful events (e.g., illness, trauma, and surgery) increase the risk for both hyperglycemia and hypoglycemia among individuals with diabetes. In severe cases, they may precipitate diabetic ketoacidosis or a nonketotic hyperglycemic hyperosmolar state, life-threatening conditions that require immediate medical care. Any individuals with diabetes experiencing illness or other stressful events should be assessed for the need for more frequent monitoring of glucose; ketosis-prone individuals also require urine or blood ketone monitoring. Clinicians should reevaluate diabetes treatment during these events and make adjustments as appropriate. Clinicians should be aware of medication interactions that may precipitate hypoglycemia. Notably, sulfonylureas interact with a number of commonly used antimicrobials (fluoroquinolones, clarithromycin, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole) that can dramatically increase their effective dose, leading to hypoglycemia (143–145). Clinicians should consider temporarily decreasing or stopping sulfonylureas when these antimicrobials are prescribed.

For further information on management hyperglycemia in the hospital, see Section 16, "Diabetes Care in the Hospital."

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7. Diabetes Technology: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes technology is the term used to describe the hardware, devices, and software that people with diabetes use to assist with self-management, ranging from lifestyle modifications to glucose monitoring and therapy adjustments. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, patch devices, or pump (also called continuous subcutaneous insulin infusion [CSII]) and glucose as assessed by blood glucose monitoring (BGM) or continuous glucose monitoring (CGM). Diabetes technology has expanded to include automated insulin delivery (AID) systems, where CGM-informed algorithms modulate insulin delivery, connected insulin pens, as well as diabetes self-management support software serving as medical devices. Diabetes technology, when coupled with education, follow-up, and support, can improve the lives and health of people with diabetes; however, the complexity and rapid evolution of the diabetes technology landscape can also be a barrier to implementation for people with diabetes, their care partners, and the health care team.

GENERAL DEVICE PRINCIPLES

Recommendations

7.1 Diabetes devices should be offered to people with diabetes. **A**

7.2 Initiation of continuous glucose monitoring (CGM) should be offered to people with type 1 diabetes early in the disease, even at time of diagnosis. **A**

7.3 Consider establishing competencies based on role in practice setting for health care professionals working with diabetes technology. **E**

7.4 The type(s) and selection of devices should be individualized based on a person's specific needs, preferences, and skill level. In the setting of an individual whose diabetes is partially or wholly managed by someone else (e.g., a young child or a person with cognitive impairment or dexterity, psychosocial, and/or physical limitations), the caregiver's skills and preferences are integral to the decision-making process. **E**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

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7.5 When prescribing a device, ensure that people with diabetes and caregivers receive initial and ongoing education and training, either in person or remotely, and ongoing evaluation of technique, results, and the ability to utilize data, including uploading/sharing data (if applicable), to monitor and adjust therapy. **C**

7.6 People with diabetes who have been using CGM, continuous subcutaneous insulin infusion (CSII), and/or automated insulin delivery (AID) for diabetes management should have continued access across third-party payers, regardless of age or A1C levels. **E**

7.7 Students should be supported at school in the use of diabetes technology, such as CGM systems, CSII, connected insulin pens, and AID systems, as recommended or prescribed by their health care team. **E**

7.8 Initiation of CSII and/or AID early, even at diagnosis, in the treatment of diabetes can be beneficial depending on a person's or caregiver's needs and preferences. **C**

Technology is rapidly changing, but there is no one-size-fits-all approach to technology use in people with diabetes. Insurance coverage can lag behind device availability, people's interest in devices and willingness for adoption can vary, and health care teams may have challenges in keeping up with newly released technology. An American Diabetes Association resource, which can be accessed at consumerguide.diabetes.org, can help health care professionals and people with diabetes make decisions as to the initial choice of devices. Other sources, including health care professionals and device manufacturers, can help people troubleshoot when difficulties arise (1–10).

Education and Training

In general, no device used in diabetes management works optimally without education, training, and ongoing support. There are multiple resources for online tutorials and training videos as well as written material on the use of devices. People with diabetes vary in comfort level with technology, and some prefer in-person training and support. Those with more education regarding device use have better outcomes (1,2); therefore, the need for additional education should be periodically assessed, particularly if outcomes are not being met. Better outcomes cannot be achieved, however, without the training and education of health care professionals. The assessment of competencies in diabetes technology is crucial for prescribers, certified diabetes and education specialists, pharmacists, nurses, and anyone involved in the care of people with diabetes. These competencies are described as basic, fundamental, intermediate, and advanced and are specific to the role of each health care team member (11). In addition, the health care team's knowledge and competency are even more relevant when people with diabetes are started on advanced diabetes technologies, such as AID systems. In such situations, training is vital and should include a discussion about realistic expectations for the ability of the initiated system to achieve glucose goals, the system's features and limitations, and the best way to utilize the new system to maximize the benefits it can offer (12).

Use in Schools

Instructions for device use should be outlined in the student's diabetes medical management plan (DMMP). A backup plan should be included in the DMMP for potential device failure (e.g., BGM, CGM, and/or insulin delivery devices). School nurses and designees should complete training to stay up to date on diabetes technologies prescribed for use in the school setting. Updated resources to support diabetes care at school, including training materials and a DMMP template, can be found online at diabetes.org/safeatschool.

Initiation of Device Use

The use of CGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management (3,4). This allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent BGM. In addition, early CGM initiation after diagnosis of type 1 diabetes in youth has been shown to decrease A1C levels and is associated with high parental satisfaction and reliance on this technology for diabetes management (5,6). Training on alarm/alert settings when initiating CGM is crucial to avoid alarm overload. In appropriate individuals, early use of AID systems or insulin pumps may be considered. Interruption of access to CGM is associated with a worsening of outcomes (7,13); therefore, it is important for individuals on CGM to have consistent access to devices.

BLOOD GLUCOSE MONITORING

Recommendations

7.9 People with diabetes should be provided with blood glucose monitoring (BGM) devices as indicated by their circumstances, preferences, and treatment. People using CGM devices must also have access to BGM at all times. **A**

7.10 People who are taking insulin and using BGM should be encouraged to check their blood glucose levels when appropriate based on their insulin therapy. This may include checking when fasting, prior to meals and snacks, after meals, at bedtime, in the middle of the night, prior to, during, and after exercise, when hypoglycemia is suspected, after treating low blood glucose levels until they are normoglycemic, when hyperglycemia is suspected, and prior to and while performing critical tasks such as driving. **B**

7.11 Health care professionals should be aware of the differences in accuracy among blood glucose meters. Only meters approved by the U.S. Food and Drug Administration (FDA) (or comparable regulatory agencies for other geographical locations) with proven accuracy should be used, with unexpired test strips purchased from a pharmacy or licensed distributor and properly stored. **E**

7.12 Although BGM in people on noninsulin therapies has not consistently shown clinically significant reductions in A1C levels, it may be helpful when altering meal plans, physical activity plans, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. **E**

7.13 Health care professionals should be aware of medications and other factors that can interfere with glucose meter accuracy and provide clinical management as indicated. **E**

Major clinical trials of insulin-treated people with diabetes have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic management on diabetes complications (14). BGM is thus an integral component of effective therapy for individuals using insulin. In recent years, CGM has emerged as a method for the assessment of glucose levels (discussed below). Glucose monitoring allows people with diabetes to evaluate their individual responses to therapy and assess whether glycemic goals are being safely achieved. Integrating results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, or adjusting medications (particularly prandial insulin doses or correction bolus doses). The specific needs and goals of the person with diabetes should dictate BGM frequency and timing or the consideration of CGM use. As recommended by the device manufacturers and the U.S. Food and Drug Administration (FDA), people with diabetes using CGM must have access to BGM for multiple reasons, including whenever there is suspicion that the CGM is inaccurate, while waiting for warm-up, when there is a disruption in CGM transmission, for calibration (if needed) or if a warning message appears, when CGM supplies are delayed, and in any clinical setting where glucose levels are changing rapidly (>2 mg/dL/min), which could cause a discrepancy between CGM and blood glucose values.

Meter Standards

Glucose meters meeting FDA guidance for meter accuracy provide the most reliable data for diabetes management. There are several current standards for the accuracy of blood glucose meters, but the two most used are those of the International Organization for Standardization (ISO) (ISO 15197:2013) and the FDA. The current ISO and FDA standards are compared in **Table 7.1**. In Europe, currently marketed meters must meet current ISO standards. In the U.S., currently marketed meters must meet the standard under which they were approved, which may not be the current standard. Moreover, the monitoring of current accuracy postmarketing is left to the manufacturer and not routinely checked by an independent source.

People with diabetes assume their glucose meter is accurate because it is FDA cleared, but that may not be the case. There is substantial variation in the accuracy of widely used BGM systems (15,16). The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for BGM (diabetestechnology.org/surveillance/). In one analysis, 6 of the top 18 best-selling glucose meters met the accuracy standard (17). In a subsequent analysis with updated glucose meters, 14 of 18 glucose meters met the minimum accuracy requirements (18). There are single-meter studies in which benefits have been found with individual meter systems, but few studies have compared meters head-to-head. Certain meter system characteristics, such as the use of lancing devices that are less painful (19) and the ability to reapply blood to a strip with an insufficient initial sample, or meters with integrated speech that can read aloud glucose levels for visually impaired individuals (20), may also be beneficial to people with diabetes (21) and may make BGM less burdensome to perform.

Counterfeit Strips

People with diabetes should be advised against purchasing or reselling preowned or secondhand test strips, as these may give incorrect results. Only unopened and unexpired vials of glucose test strips should be used to ensure BGM accuracy.

Optimizing Blood Glucose Monitoring Device Use

Optimal use of BGM devices requires proper review and interpretation of data by both the person with diabetes and the health care professional to ensure that data are used in an effective and timely manner. In people with type 1 diabetes, there is a correlation between greater BGM frequency and lower A1C levels (22). Among those who check their blood glucose at least once daily, many report taking no action when results are high or low (23). Some meters now provide advice to the user in real time when monitoring glucose levels (24), whereas others can be used as a part of integrated health platforms (25). People with diabetes should be taught how to use BGM data to adjust food intake, physical activity, or pharmacologic therapy to achieve specific goals. The ongoing need for and frequency of BGM should be reevaluated at each routine visit to ensure its effective use (22,26,27).

People With Diabetes on Intensive Insulin Therapies

BGM is especially important for people with diabetes treated with insulin to monitor for and prevent hypoglycemia and hyperglycemia. Most individuals on intensive insulin therapies (multiple daily injections [MDI] or insulin pump therapy) should be encouraged to assess glucose levels using BGM (and/or CGM) prior to meals and snacks, at bedtime, occasionally postprandially, prior to, during, and

Table 7.1—Comparison of ISO 15197:2013 and FDA BG meter accuracy standards

Setting	FDA (287,299)	ISO 15197:2013 (300)
Hospital use	95% within 12% for BG $\geq$75 mg/dL 95% within 12 mg/dL for BG $<$75 mg/dL 98% within 15% for BG $\geq$75 mg/dL 98% within 15 mg/dL for BG $<$75 mg/dL	95% within 15% for BG $\geq$100 mg/dL 95% within 15 mg/dL for BG $<$100 mg/dL 99% in A or B region of consensus error grid‡
Home use	95% within 15% for all BG in the usable BG range† 99% within 20% for all BG in the usable BG range†	

BG, blood glucose; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization. To convert mg/dL to mmol/L, see endmemo.com/medical/unitconvert/Glucose.php. †The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error). ‡Values outside of the “clinically acceptable” A and B regions are considered “outlier” readings and may be dangerous to use for therapeutic decisions (301).

after physical activity, when they suspect hypoglycemia or hyperglycemia, after treating hypoglycemia until they are normoglycemic, and prior to and while performing critical tasks such as driving. For many individuals using BGM, this requires checking up to 6–10 times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjusting for multiple confounders, increased daily frequency of BGM was significantly associated with lower A1C levels (−0.2% per additional check per day) and with fewer acute complications (28).

People With Diabetes Using Basal Insulin and/or Oral Agents and Noninsulin Injectables

The evidence is insufficient regarding when to prescribe BGM and how often monitoring is needed for insulin-treated people with diabetes who do not use intensive insulin therapy, such as those with type 2 diabetes taking basal insulin with or without oral agents and/or noninsulin injectables. However, for those taking basal insulin, assessing fasting glucose with BGM to inform dose adjustments to achieve blood glucose targets results in lower A1C levels (29,30).

In people with type 2 diabetes not taking insulin, routine glucose monitoring may be of limited additional clinical benefit. By itself, even when combined with education, this practice has shown limited improvement in outcomes (31–34). However, for some individuals, glucose monitoring can provide insight into the impact of nutrition, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals (for more details, see Section 2, "Diagnosis and Classification of Diabetes"). It may be useful when coupled with a treatment adjustment program. In a year-long study of insulin-naive people with diabetes with suboptimal initial glycemic outcomes, a group trained in structured BGM (a paper tool was used at least quarterly to collect and interpret seven-point BGM profiles taken on three consecutive days) reduced their A1C levels by 0.3% more than that of the control group (35). A trial of once-daily BGM that included enhanced feedback from people with diabetes through messaging found no clinically or statistically significant change in A1C levels at 1 year (34). Meta-analyses have suggested that BGM can reduce A1C levels by 0.25–0.3% at 6 months (36–38), but the effect was attenuated at 12 months in one analysis (36). Reductions in A1C levels were greater (−0.3%) in trials where structured BGM data were used to adjust medications, but A1C levels were not changed significantly without such structured diabetes therapy adjustment (38). A key consideration is that performing BGM alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management treatment plans.

Glucose Meter Inaccuracy

Although many meters function well under various circumstances, health care professionals and people with diabetes must be aware of factors that impair meter accuracy. A meter reading that seems discordant with the clinical picture needs to be retested or tested in a laboratory. Health care professionals in intensive care unit settings need to be particularly aware of the potential for incorrect meter readings during critical illness, and laboratory-based values should be used if there is any doubt. Some meters give error messages if meter readings are likely to be false (39).

Oxygen. Currently available glucose monitors use an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase (40). Glucose oxidase monitors are sensitive to the oxygen available and should only be used with capillary blood in people with normal oxygen saturation. Higher oxygen tensions (i.e., arterial blood or oxygen therapy) may result in false low-glucose readings, and low oxygen tensions (i.e., high altitude, hypoxia, or venous blood readings) may lead to falsely elevated glucose readings. Glucose dehydrogenase–based monitors are generally not sensitive to oxygen.

Temperature. Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range (40). Most will show an error if the temperature is unacceptable, but a few will provide a reading and a message indicating that the value may be incorrect. Humidity and altitude may also alter glucose readings.

Table 7.2—Interfering substances for glucose meter readings

Glucose oxidase monitors
Uric acid
Galactose
Xylose
Acetaminophen
L-DOPA
Ascorbic acid
Glucose dehydrogenase monitors using pyrroloquinolinequinone cofactor (GDH/PQQ)
Icodextrin (used in peritoneal dialysis)

Interfering Substances. There are a few physiologic and pharmacologic factors that interfere with glucose readings. Most interfere only with glucose oxidase systems (40). They are listed in **Table 7.2**.

CONTINUOUS GLUCOSE MONITORING DEVICES

See **Table 7.3** for definitions of types of CGM devices.

Recommendations

7.14 Real-time CGM (rtCGM) **A** or intermittently scanned CGM (isCGM) **B** should be offered for diabetes management in adults with diabetes on multiple daily injections (MDI) or CSII who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.15 rtCGM **A** or isCGM **B** should be offered for diabetes management in adults with diabetes on basal insulin who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.16 rtCGM **A** or isCGM **E** should be offered for diabetes management in youth with type 1 diabetes on MDI or CSII who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.17 rtCGM or isCGM should be offered for diabetes management in youth with type 2 diabetes on MDI or CSII who are capable of using the devices safely (either by themselves or with a caregiver).

Table 7.3—Continuous glucose monitoring devices

Type of CGM	Description
rtCGM	CGM systems that measure and display glucose levels continuously
isCGM with and without alarms	CGM systems that measure glucose levels continuously but require scanning for visualization and storage of glucose values
Professional CGM	CGM devices that are placed on the person with diabetes in the health care professional's office and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. Unlike rtCGM and isCGM devices, these devices are clinic-based and not owned by the person with diabetes.

CGM, continuous glucose monitoring; isCGM, intermittently scanned CGM; rtCGM, real-time CGM.

The choice of device should be made based on the individual's circumstances, preferences, and needs. **E**

7.18 In people with diabetes on MDI or CSII, rtCGM devices should be used as close to daily as possible for maximal benefit. **A** isCGM devices should be scanned frequently, at a minimum once every 8 h to avoid gaps in data. **A** People with diabetes should have uninterrupted access to their supplies to minimize gaps in CGM. **A**

7.19 When used as an adjunct to preprandial and postprandial BGM, CGM can help to achieve A1C targets in diabetes and pregnancy. **B**

7.20 Periodic use of rtCGM or isCGM or use of professional CGM can be helpful for diabetes management in circumstances where consistent use of CGM is not desired or available. **C**

7.21 Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. **E**

7.22 People who wear CGM devices should be educated on potential interfering substances and other factors that may affect accuracy. **C**

CGM measures interstitial glucose (which correlates well with plasma glucose, although at times, it can lag if glucose levels are rising or falling rapidly). There are two basic types of CGM devices. The first type includes those that are owned by the user, unblinded, and intended for frequent or continuous use, including real-time CGM (rtCGM) and intermittently scanned CGM (isCGM). The second type is professional CGM devices that are owned by practices and applied in the clinic, which provide data that are blinded or unblinded for a discrete period of time. The types of sensors currently available are either disposable (rtCGM and isCGM) or implantable (rtCGM). **Table 7.3** provides the definitions for the types of CGM devices. For people with type 1 diabetes using CGM, frequency of sensor use is an important predictor of A1C lowering for all age-groups (41,42). The frequency of scanning with isCGM devices is also correlated with improved outcomes (43–46).

Some real-time systems require calibration by the user, which varies in frequency depending on the device. Additionally, some CGM systems are called adjunctive, meaning the user should perform BGM for making treatment decisions such as dosing insulin or treating hypoglycemia. Devices that do not have this requirement outside of certain clinical situations (see Blood Glucose Monitoring, above) are called nonadjunctive (47–49).

One specific isCGM device (Freestyle Libre 2 [no generic form available]) and three specific rtCGM devices (Dexcom G6 [no generic form available], Dexcom G7 [no generic form available], and FreeStyle Libre 3 [no generic form available]) have been designated integrated CGM (iCGM) devices (50). This is a higher standard set by the FDA so that these devices can be integrated with other digitally connected devices. Dexcom G6 rtCGM, Dexcom G7 rtCGM, and a modified version of Libre 2 and Libre 3 are FDA approved for use with AID systems. At this time, Dexcom G6 is integrated with four AID systems (t:slim ×2 with control IQ, Omnipod 5, iLet, and Mobi). Similarly, the Medtronic Guardian 3 rtCGM (no generic available) and the Medtronic Guardian 4 rtCGM are FDA approved for use with the 670/770G and 780G AID systems, respectively.

Benefits of Continuous Glucose Monitoring

Data From Randomized Controlled Trials

Multiple randomized controlled trials (RCTs) have been performed using rtCGM devices, and the results have largely been positive in terms of reducing A1C levels and/or episodes of hypoglycemia, as long as participants regularly wore the devices (41,42,51–73). The initial studies were done primarily in adults and youth with type 1 diabetes on insulin pump therapy and/or MDI (41,42,51–54,57–67). The primary outcome was met and showed benefit in adults of all ages (41,51,52,57, 58,60,62,63,74–77), including seniors (59, 78,79). Data in children show that rtCGM use in young children with type 1 diabetes reduced hypoglycemia; in addition, behavioral support of parents of young children with diabetes using rtCGM showed the benefits of reducing hypoglycemia concerns and diabetes distress (41,66,80). Similarly, A1C level reduction was seen in adolescents and young adults with type 1 diabetes using rtCGM (65). RCT data on rtCGM use in individuals with type 2 diabetes on MDI (69), mixed therapies (70,71), and basal insulin (72,81) have consistently shown reductions in A1C levels and increases in time in range (TIR) (70–180 mg/dL [3.9–10 mmol/L]) but not a reduction in rates of hypoglycemia. The improvements in type 2 diabetes have largely occurred without changes in insulin doses or other diabetes medications. CGM discontinuation in individuals with type 2 diabetes on basal insulin caused partial reversal of A1C reduction and TIR improvements, suggesting that continued CGM use achieves the greatest benefits (13). In addition, rtCGM benefits were reported in a mixed population (including people not using insulin) of adults with type 2 diabetes with reduction in A1C levels, increase in TIR, and reduction of time in hyperglycemia ($>$180 mg/dL [$>$10 mmol/L] and $>$250 mg/dL [$>$13.8 mmol/L]) (10).

RCT data for isCGM are fewer but increasing. One study was performed in adults with type 1 diabetes and met its primary outcome of a reduction in rates of hypoglycemia (55). In adults with type 2 diabetes using insulin, two studies were done: one study did not meet its primary end point of A1C levels reduction (82) but achieved a secondary end point of a reduction in hypoglycemia, and the other study met its primary end point of an improvement in the Diabetes Treatment Satisfaction Questionnaire score as well as a secondary end point of A1C level reduction (83). In a study of individuals with type 1 or type 2 diabetes taking insulin, the primary outcome of a reduction in severe hypoglycemia was not met and the incidence of severe hypoglycemia was not significantly different between isCGM users and the BGM group (84). One study in youth with type 1 diabetes did not show a reduction in A1C levels (85); however, the device was well received and was associated with an increased frequency of testing and improved diabetes treatment satisfaction (85). A randomized trial of adults with type 1 diabetes showed that the use of isCGM with optional alerts and alarms resulted in reduction of A1C levels compared with BGM use (9). The benefits of isCGM for adults with type 2 diabetes not using insulin were recently reported in an RCT. In this study, the use of isCGM plus diabetes education versus diabetes education alone showed decreased A1C levels and increased TIR as well as increased time in tight target range (70–140 mg/dL [3.9–7.8 mmol/L]) in the isCGM-plus-education group (8).

Observational and Real-world Studies

isCGM has been widely available in many countries for people with diabetes, and this allows for the collection of large amounts of data across groups of people with diabetes. In adults with diabetes, these data include results from observational studies, retrospective studies, and analyses of registry and population data (86,87). In individuals with type 1 diabetes wearing isCGM devices, most (46,86,88), but not all (89), studies have shown improvement in A1C levels. Reductions in acute diabetes complications, such as diabetic ketoacidosis (DKA), episodes of severe hypoglycemia or diabetes-related coma, and hospitalizations for hypoglycemia and hyperglycemia, have been observed (46,89,90), with persistent effects observed even after 2 years of CGM initiation (91). Some retrospective/observational data have shown an improvement in A1C levels for adults with type 2 diabetes on MDI (92), basal insulin (93), and basal insulin or noninsulin therapies (94). In a retrospective study of adults with type 2 diabetes taking insulin, a reduction in acute diabetes-related events and all-cause hospitalizations was seen (95). Results of self-reported outcomes varied, but where measured, people with diabetes had an increase in treatment satisfaction with isCGM compared with BGM.

In an observational study in youth with type 1 diabetes, a slight increase in A1C levels and weight was seen, but the device was associated with a high user satisfaction rate (87).

Retrospective data from rtCGM use in a Veterans Affairs population (96) with type 1 and type 2 diabetes treated with insulin showed that the use of rtCGM significantly lowered A1C levels and reduced rates of emergency department visits or hospitalizations for hypoglycemia but did not significantly lower overall rates of emergency department visits, hospitalizations, or hyperglycemia.

Real-time Continuous Glucose Monitoring Compared With Intermittently Scanned Continuous Glucose Monitoring

In adults with type 1 diabetes, three RCTs have been conducted comparing isCGM and rtCGM (97–99). In two of the studies, the primary outcome was a reduction in time spent in hypoglycemia, and rtCGM showed greater benefits compared with isCGM (97,98). In the other study, the primary outcome was improved TIR, and rtCGM also showed greater benefits compared with isCGM (99). A retrospective analysis also showed improvement in TIR with rtCGM compared with isCGM (100). A more recent 12-month real-world nonrandomized study compared rtCGM with isCGM in adults with type 1 diabetes. At 12 months, A1C levels, time in level 1 hypoglycemia ($<$70 mg/dL [$<$3.9 mmol/L]), and time in level 2 hypoglycemia ($<$54 mg/dL [$<$3.0 mmol/L]) were all lower in the rtCGM group than in the isCGM group; similarly, the TIR was higher in the rtCGM group than in the isCGM group (101).

Data Analysis

The abundance of data provided by CGM offers opportunities to analyze data for people with diabetes more granularly than previously possible, providing additional information to aid in achieving glycemic goals. A variety of metrics have been proposed (102) and are discussed in Section 6, “Glycemic Goals and Hypoglycemia.” CGM is essential for creating an ambulatory glucose profile and providing data on TIR, percentage of time spent above and below range, and glycemic variability (103). Data analysis can be burdensome without a systematic approach to its review. Several efforts have been made to streamline the interpretation of CGM reports to assist health care professionals in their daily practice. These have various, but overall similar, approaches. The initial steps are focused on assessing the sufficiency and quality of data; subsequent recommendations include reviewing the presence and trends or patterns of hypoglycemia, followed by hyperglycemia patterns and trends. Some authors also suggest approaches to changing therapy plans based on the data reviewed that enable health care professionals to make a simple yet comprehensive review and plan of care even within the time constraints of office visits (104–108).

Real-time Continuous Glucose Monitoring Device Use in Pregnancy

Recently, CGM indication has been expanded to include pregnancy for Dexcom G7, FreeStyle Libre 2, and FreeStyle Libre 3, which will enhance care in this population (109,110). Prior data from one well-designed RCT showed a reduction in A1C levels in pregnant adults with type 1 diabetes on MDI or insulin pump therapy and using rtCGM in addition to standard care; CGM users experienced more pregnancy-specific TIR (63–140 mg/dL [3.5–7.8 mmol/L]) and less time in hyperglycemia (111). This study demonstrated the value of rtCGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C levels and a significant improvement in the maternal glucose TIR for pregnancy (63–140 mg/dL [3.5–7.8 mmol/L]), without an increase in hypoglycemia, as well as reductions in large-for-gestational-age births, infant hospital length of stay, and severe neonatal hypoglycemia (111). An observational cohort study that evaluated the glycemic variables reported using rtCGM and isCGM found that lower mean glucose, lower standard deviation, and a higher percentage of TIR were associated with lower risks of large-for-gestational-age births and other adverse neonatal outcomes (112). Data from one study suggested that the use of rtCGM-reported mean glucose is superior to use of the glucose management indicator and other calculations to estimate A1C levels given the changes to A1C levels that occur in pregnancy (113). Two studies employing intermittent use of rtCGM showed no difference in neonatal outcomes in individuals with type 1 diabetes (114) or gestational diabetes mellitus (115). At this time, data are insufficient for recommending the use of CGM in all pregnant people with type 2 diabetes or GDM (116,117). The decision of whether to use CGM in pregnant individuals with type 2 diabetes or GDM should be individualized based on treatment plan, circumstances, preferences, and needs. Although CGM systems for use in pregnancy do not require calibrations and are approved for nonadjunctive use, when using CGM in diabetes and pregnancy, determination of glucose levels by finger stick may be necessary in certain circumstances, such as in the setting of hypoglycemia or hyperglycemia outside the recommended CGM targets (63–140 mg/dL [3.5–7.8 mmol/L]) during pregnancy.

Use of Professional and Intermittent Continuous Glucose Monitoring

Professional CGM devices, which provide retrospective data, either blinded or unblinded, for analysis can be used to identify patterns of hypoglycemia and hyperglycemia (118,119). Professional CGM can be helpful to evaluate an individual's glucose levels when either rtCGM or isCGM is not available to the individual or they prefer a blinded analysis or a shorter experience with unblinded data. It can be particularly useful in individuals using agents that can cause hypoglycemia, as the data can be used to evaluate periods of hypoglycemia and make medication dose adjustments if needed. It can also be useful to evaluate periods of hyperglycemia.

Some data have shown the benefit of intermittent use of CGM (rtCGM or isCGM) in individuals with type 2 diabetes on noninsulin and/or basal insulin therapies (70,120). In these RCTs, people with type 2 diabetes not on intensive insulin therapy used CGM intermittently compared with those randomized to BGM. Both early (70) and late improvements in A1C levels were found (70,120). Use of professional or intermittent CGM should always be coupled with analysis and interpretation for people with diabetes, along with education as needed to adjust medication and change lifestyle behaviors (121–123).

Side Effects of Continuous Glucose Monitoring Devices

Contact dermatitis (both irritant and allergic) has been reported with all devices that attach to the skin (18,124,125). In some cases, this has been linked to the presence of isobornyl acrylate, a skin sensitizer that can cause an additional spreading allergic reaction (126–128). It is important to ask CGM users periodically about adhesive reactions, as tape formulations may change over time. Patch testing can sometimes identify the cause of contact dermatitis (129). Identifying and eliminating tape allergens is important to ensure the comfortable use of devices and promote self-care (130–133). The Panther Program offers resources in English and Spanish at pantherprogram.org/skin-solutions. In some instances, using an implanted sensor can help avoid skin reactions in those sensitive to tape (134,135).

Substances and Factors Affecting Continuous Glucose Monitoring Accuracy

Sensor interference due to several medications/substances is a known potential source of CGM sensor measurement errors (**Table 7.4**). While several of these substances have been reported in the various CGM brands' user manuals, additional interferences have been discovered after the market release of these products. Hydroxyurea, used for myeloproliferative disorders and hematologic conditions, is one of the most recently identified interfering substances that cause a temporary increase in sensor glucose values discrepant from actual glucose values (136–141). Similarly, substances such as mannitol and sorbitol, when administered intravenously or as a component of peritoneal dialysis solution, may increase blood mannitol or sorbitol concentrations and cause falsely elevated readings of sensor glucose (142). Therefore, it is crucial to routinely review the medications and supplements used by the person with diabetes to identify possible interfering substances and advise them accordingly on the need to use additional BGM if sensor values are unreliable due to these substances.

INSULIN DELIVERY

Insulin Syringes and Pens

Recommendations

7.23 For people with insulin-requiring diabetes on MDI, insulin pens are preferred in most cases. Still, insulin syringes may be used for insulin delivery considering individual and caregiver preference, insulin type, availability in vials, dosing

Table 7.4—Continuous glucose monitoring devices interfering substances

Medication	Systems affected	Effect
Acetaminophen		
>4 g/day	Dexcom G6, Dexcom G7	Higher sensor readings than actual glucose
Any dose	Medtronic Guardian	Higher sensor readings than actual glucose
Ascorbic acid (vitamin C), >500 mg/day	FreeStyle Libre 14 day, FreeStyle Libre 2, FreeStyle Libre 3	Higher sensor readings than actual glucose
Hydroxyurea	Dexcom G6, Dexcom G7, Medtronic Guardian	Higher sensor readings than actual glucose
Mannitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose
Sorbitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose

therapy, cost, and self-management capabilities. **C**

7.24 Insulin pens or insulin injection aids are recommended for people with dexterity issues or vision impairment or when decided by shared decision-making to facilitate the accurate dosing and administration of insulin. **C**

7.25 Connected insulin pens can be helpful for diabetes management and may be used in people with diabetes taking subcutaneous insulin. **E**

7.26 FDA-approved insulin dose calculators/decision support systems may be helpful for calculating insulin doses. **C**

Injecting insulin with a syringe or pen (143–159) is the insulin delivery method used by most people with diabetes (149,160), although inhaled insulin is also available. Others use insulin pumps or AID devices (see INSULIN PUMPS AND AUTOMATED INSULIN DELIVERY SYSTEMS, below). For people with diabetes who use insulin, insulin syringes and pens are both able to deliver insulin safely and effectively for the achievement of glycemic targets. Individual preferences, cost, insulin type, dosing therapy, and self-management capabilities should be considered when choosing among delivery systems. Trials with insulin pens generally show equivalence or small improvements in glycemic outcomes compared with using a vial and syringe. Many individuals with diabetes prefer using a pen because of its simplicity and convenience. It is important to note that while many insulin types are available for purchase as either pens or vials, others may be available in only one form or the other, and there may be significant cost differences between pens and vials (see **Table 9.4** for a list of insulin product costs with dosage forms). Insulin pens may allow people with vision impairment or dexterity issues to dose insulin accurately (161–163), and insulin injection aids are also available to help with these issues. (For a helpful list of injection aids, see consumerguide.diabetes.org/collections/injection-aids). Inhaled insulin can be useful in people who have an aversion to injection.

The most common syringe sizes are 1 mL, 0.5 mL, and 0.3 mL, allowing doses of up to 100 units, 50 units, and 30 units, respectively, of U-100 insulin. Some 0.3-mL syringes have half-unit markings, whereas other syringes have 1- to 2-unit increment markings. In a few parts of the world, insulin syringes still have U-80 and U-40 markings for older insulin concentrations and veterinary insulin, and U-500 syringes are available for the use of U-500 insulin. Syringes are generally used once but may be reused by the same individual in resource-limited settings with appropriate storage and cleansing (163).

Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. Pens vary with respect to dosing increment and minimal dose, ranging from half-unit doses to 2-unit dose increments, with the latter available in U-200 insulin pens. U-500 pens come in 5-unit dose increments. Some reusable pens include a memory function, which can recall dose amounts and timing. Connected insulin pens are insulin pens with the capacity to record and/or transmit insulin dose data. Insulin pen caps are also available and are placed on existing insulin pens and may assist with calculating insulin doses and by providing a memory function. Some connected insulin pens and pen caps can be programmed to calculate insulin doses, can be synced with select CGM systems, and can provide downloadable data reports. These pens and pen caps are useful to people with diabetes for real-time insulin dosing and allow clinicians to retrospectively review the insulin delivery times and in some cases doses and glucose data in order to make informed insulin dose adjustments (164). A quantitative study showed that people with diabetes preferred connected pens because of their ability to log insulin doses and glucose levels automatically (164).

Needle thickness (gauge) and length are other considerations. Needle gauges range from 22 to 34, with a higher gauge indicating a thinner needle. A thicker needle can give a dose of insulin more quickly, while a thinner needle may cause less pain. Needle length ranges from 4 to 12.7 mm, with some evidence suggesting that shorter needles (4–5 mm) lower the risk of intramuscular injection with erratic absorption and possibly the development of lipohypertrophy. When reused, needles may be duller and thus injections may be more painful. Proper insulin injection technique is a requisite for receiving the full dose of insulin with each injection. Concerns with technique and use of the proper technique are outlined in Section 9, “Pharmacologic Approaches to Glycemic Treatment.”

Bolus calculators have been developed to aid dosing decisions (165–170). These systems are subject to FDA approval to ensure safety and efficacy in terms of algorithms used and subsequent dosing recommendations. People interested in using these systems should be encouraged to use those that are FDA approved. Health care professional input and education can be helpful for setting the initial dosing calculations with ongoing follow-up for adjustments as needed.

Insulin Pumps and Automated Insulin Delivery Systems

Recommendations

7.27 AID systems should be offered for diabetes management to youth and adults with type 1 diabetes **A** and other types of insulin-deficient diabetes **E** who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual’s circumstances, preferences, and needs. **A**

7.28 Insulin pump therapy alone with or without a sensor-augmented pump low-glucose suspend feature should be offered for diabetes management to youth and adults on MDI with type 1 diabetes **A** or other types of insulin-deficient diabetes **E** who are capable of using the device safely (either by themselves or with a caregiver) and are not able to use or do not choose an AID system. The choice of device should be made based on the individual’s circumstances, preferences, and needs. **A**

7.29 Insulin pump therapy can be offered for diabetes management to youth and adults on MDI with type 2 diabetes who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual’s circumstances, preferences, and needs. **A**

7.30 Individuals with diabetes who have been using CSII should have continued access across third-party payers. **E**

Insulin Pumps

Insulin pumps have been available in the U.S. for over 40 years. These devices deliver rapid-acting insulin throughout the day to help manage glucose levels. Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach directly to the skin without tubing. AID systems, which can adjust insulin delivery rates based on sensor glucose values, are preferred over nonautomated pumps and MDI in people with type 1 diabetes.

Most studies that compare MDI with insulin pump therapy have been relatively small and of short duration. However, a systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C levels (-0.30% [95% CI -0.58 to -0.02]) and for reducing severe hypoglycemia rates in children and adults (171). Real-world data on insulin pump use in individuals with type 1 diabetes show benefits in A1C levels and hypoglycemia reductions as well as total daily insulin dose reduction (172). There is no consensus to guide choosing which form of insulin administration is best for a given individual, and research to guide this decision-making process is needed (171). Thus, the choice of MDI or an insulin pump is often based upon the characteristics of the person with diabetes and which method is most likely to benefit them. DiabetesWise (diabeteswise.org/) and DiabetesWise Pro (pro.diabeteswise.org/), for health care professionals, and the PANTHER Program (pantherprogram.org/device-comparison-chart) have helpful websites to assist health care professionals and people with diabetes in choosing diabetes devices based on their individual needs and the features of the devices. Newer systems, such as sensor-augmented pumps and AID systems, are discussed below.

Adoption of pump therapy in the U.S. shows geographical variations, which may be related to health care professional preference or center characteristics (173,174) and socioeconomic status, as pump therapy is more common in individuals of higher socioeconomic status, as reflected by private health insurance, family income, and education (173,174). Given the additional barriers to optimal diabetes care observed in disadvantaged groups (175), addressing the differences in access to insulin pumps and other diabetes technologies may contribute to fewer health disparities.

Pump therapy can be successfully started at the time of diagnosis (176,177). Practical aspects of pump therapy initiation include assessment of readiness of the person with diabetes and their family, if applicable (although there is no consensus on which factors to consider in adults [178] or children and adolescents with diabetes), selection of pump type and initial pump settings, individual/family education on potential pump complications (e.g., DKA with infusion set failure), transition from MDI, and introduction of advanced pump settings (e.g., temporary basal rates and extended/square/dual-wave bolus).

Older individuals with type 1 diabetes benefit from ongoing insulin pump therapy. There are no data to suggest that measurement of C-peptide levels or antibodies predicts success with insulin pump therapy (179,180). Additionally, the frequency of follow-up does not influence outcomes. Access to insulin pump therapy, including AID systems, should be allowed or continued in older adults as it is in younger people.

Complications of the pump can be caused by issues with infusion sets (dislodgement and occlusion), which place individuals at risk for ketosis and DKA and thus must be recognized and managed early (181). Other pump skin issues include lipohypertrophy or, less frequently, lipoatrophy (182,183) and pump site infection (184). Discontinuation of pump therapy is relatively uncommon today; the frequency has decreased over the past few decades, and its causes have changed (184,185). Current reasons for attrition are problems with cost or wearability, loss of insurance, dislike for the pump, suboptimal glycemic outcomes, or mood disorders (e.g., anxiety or depression) (186).

Insulin Pumps in Youth

The safety of insulin pumps in youth has been established for over 15 years (187). Studying the effectiveness of insulin pump therapy in lowering A1C levels has been challenging because of the potential selection bias of observational studies. Participants on insulin pump therapy may have a higher socioeconomic status that may facilitate better glycemic outcomes (188) versus MDI. In addition, the fast pace of development of new insulins and technologies quickly renders comparisons obsolete. However, RCTs that compared insulin pumps and MDI with rapid-acting insulin analogs demonstrated a modest improvement in A1C levels in participants on insulin pump therapy (189,190). Observational studies, registry data, and meta-analyses have also suggested an improvement in glycemic outcomes in participants on insulin pump therapy (191–193). Data suggest that insulin pumps reduce the rates of severe hypoglycemia compared with MDI (193–196).

There is also evidence that insulin pump therapy may reduce DKA risk (193,197) and diabetes complications, particularly retinopathy and peripheral neuropathy in youth, compared with MDI (178). In addition, treatment satisfaction and quality-of-life measures improved on insulin pump therapy compared with MDI (198,199). Therefore, insulin pumps can be used safely and effectively in youth with type 1 diabetes to assist with achieving targeted glycemic outcomes while reducing the risk of hypoglycemia and DKA, improving quality of life, and preventing long-term complications. Based on shared decision-making by people with diabetes and health care professionals, insulin pumps may be considered in all children and adolescents with type 1 diabetes. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age (200). Because of a paucity of data in adolescents and youth with type 2 diabetes, there is insufficient evidence to make recommendations.

Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden (191,201).

Sensor-Augmented Pumps

Sensor-augmented pumps (or partial closed-loop systems) consist of three components: an insulin pump, a CGM system, and an algorithm that automates insulin suspension when glucose is low or is predicted to go low within the next 30 min, and these systems have been approved by the FDA. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 people with type 1 diabetes showed that sensor-augmented insulin pump therapy with a low-glucose suspend function significantly reduced nocturnal hypoglycemia over 3 months without increasing A1C levels (61). In a different sensor-augmented pump, predictive low-glucose suspend reduced time spent with glucose <70 mg/dL from 3.6% at baseline to 2.6% (3.2% with sensor-augmented pump therapy without predictive low-glucose suspend) without rebound hyperglycemia during a 6-week randomized crossover trial (202). These devices may offer the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia. Additional studies have been performed in adults and children that show the benefits of this technology (203–205).

Automated Insulin Delivery Systems

AID systems increase and decrease insulin delivery based on sensor-derived glucose levels to mimic physiologic insulin delivery. These systems consist of three components: an insulin pump, a CGM system, and an algorithm that determines insulin delivery. All AID systems on the market today adjust basal delivery in real time, and some deliver correction doses automatically. While insulin delivery in closed-loop systems eventually may be truly automated, currently used AID systems require the manual entry of carbohydrates consumed or qualitative meal estimation announcements to calculate prandial doses, and adjustments for physical activity must be announced in most systems. Multiple studies using various systems with varying algorithms, pumps, and sensors have been performed in adults and children (206–218). Evidence suggests AID systems reduce A1C levels and improve TIR (219–231). They may also lower the risk of exercise-related hypoglycemia (231) and may have psychosocial benefits (232–236). The use of AID systems depends on the preference of the person with diabetes and the selection of individuals (and/or caregivers) who are capable of safely and effectively using the devices.

The data from real-world studies on AID systems have substantiated the results observed in RCTs and have confirmed the clinical benefits of AID systems in people with type 1 diabetes. Benefits include improvement in A1C levels, TIR, and other glucometrics as well as psychosocial benefits (237–242).

Finally, real-world data showed that AID systems provide the same glycemic benefits to Medicare and Medicaid beneficiaries with type 1 and type 2 diabetes, emphasizing that access to this technology should be made available regardless of A1C levels and should be based on the individual's needs (243).

Automated Insulin Delivery Systems in Pregnancy

The use of AID systems in diabetes and pregnancy presents particular challenges, as none of the current FDA-approved systems have glucose goals that are pregnancy specific or algorithms designed to achieve pregnancy-specific glucose goals. Initiating or continuing AID systems during pregnancy needs to be assessed carefully. Selected individuals with type 1 diabetes should be evaluated as potential candidates for AID systems in the setting of expert guidance. Moreover, if the decision is made to use these systems in selected pregnant individuals, then using assistive techniques, such as the combination of sensor-augmented pump mode and hybrid closed-loop mode at different time points in pregnancy or throughout the day, should be considered and applied as needed to achieve intended goals (244). See Section 15, "Diabetes and Pregnancy," for more details.

Insulin Pumps in People With Type 2 and Other Types of Diabetes

Traditional insulin pumps can be considered for the treatment of people with type 2 diabetes who are on MDI as well as those who have other types of diabetes resulting in insulin deficiency, for instance, those who have had a pancreatectomy and/or individuals with cystic fibrosis (245–249). Similar to data on insulin pump use in people with type 1 diabetes, reductions in A1C levels have been reported in some studies (247,250). More recently, real-world reports have shown reduction of A1C levels and reduction of total daily insulin dose in individuals with type 2 diabetes initiating insulin pump therapy (251). Use of insulin pumps in insulin-requiring people with any type of diabetes may improve user satisfaction and simplify therapy (180,245).

For people with diabetes judged to be clinically insulin deficient who are treated with an intensive insulin therapy, the presence or absence of measurable C-peptide levels does not correlate with response to therapy (180). A low C-peptide value should not be required for insulin pump coverage in individuals with type 2 diabetes.

The use of insulin pumps and AID systems in type 2 diabetes is still limited; however, real-world studies have shown benefits of these technologies in these individuals (243,252).

Alternative insulin delivery options in people with type 2 diabetes may include disposable patch-like devices, which provide either a CSII of rapid-acting insulin (basal) with bolus insulin in 2-unit increments at the press of a button or bolus insulin only delivered in 2-unit increments used in conjunction with basal insulin injections (246,248,253,254). Use of an insulin pump as a means of insulin delivery is an individual choice for people with diabetes and should be considered an option in those who are capable of safely using the device.

Do-It-Yourself Closed-Loop Systems

Recommendation

7.31 Individuals with diabetes may be using systems not approved by the FDA, such as do-it-yourself closed-loop systems and others; health care professionals cannot prescribe these systems but should assist in diabetes management to ensure the safety of people with diabetes. **E**

Some people with type 1 diabetes have been using do-it-yourself systems that combine an insulin pump and an rtCGM with a controller and an algorithm designed to automate insulin delivery (255–259). Data are emerging on the safety and effectiveness of specific systems (260,261). However, these systems are not approved by the FDA, although efforts are underway to obtain regulatory approval for some of them. The information on how to set up and manage these systems is freely available on the internet, and there are internet groups where people inform each other as to how to set up and use them. Although health care professionals cannot prescribe these systems, it is crucial to keep people with diabetes safe if they are using these methods for AID. Part of this entails ensuring people have a backup plan in case of pump failure. Additionally, in most do-it-yourself systems, insulin doses are adjusted based on the pump settings for basal rates, carbohydrate ratios, correction doses, and insulin activity. Therefore, these settings can be evaluated and modified based on the individual's insulin requirements.

Digital Health Technology

Recommendation

7.32 Systems that combine technology and online coaching can be beneficial in managing prediabetes and diabetes for some individuals. **B**

Increasingly, people are turning to the internet for advice, coaching, connection, and health care. Diabetes, partly because it is both common and numeric, lends itself to the development of apps and online programs. Recommendations for developing and implementing a digital diabetes clinic have been published (262). The FDA approves and monitors clinically validated, digital, and usually online health technologies intended to treat a medical or psychological condition; these are known as digital therapeutics or "digiceuticals" (fda.gov/medical-devices/digital-health-center-excellence/device-software-functions-including-mobile-medical-applications) (263). Other applications, such as those that assist in displaying or storing data, encourage a healthy lifestyle or provide limited clinical data support. Therefore, it is possible to find apps that have been fully reviewed and approved by the FDA and others designed and promoted by people with relatively little skill or knowledge in the clinical treatment of diabetes. There are insufficient data to provide recommendations for specific apps for diabetes management, education, and support in the absence of RCTs and validation of apps unless they are FDA cleared.

An area of particular importance is that of online privacy and security. Established cloud-based data aggregator programs, such as Tidepool, Glooko, and others, have been developed with appropriate data security features and are compliant with the U.S. Health Insurance Portability and Accountability Act of 1996. These programs can help monitor people with diabetes and provide access to their health care teams (264). Consumers should read the policy regarding data privacy and sharing before entering data into an application and learn how they can control the way their data will be used (some programs offer the ability to share more or less information, such as being part of a registry or data repository or not).

Many online programs offer lifestyle counseling to achieve weight loss and increased physical activity (265). Many include a health coach and can create small groups of similar participants on social networks. Some programs aim to treat prediabetes and prevent progression to diabetes, often following the model of the Diabetes Prevention Program (266,267). Others assist in improving diabetes outcomes by remotely monitoring clinical data (for instance, wireless monitoring of glucose levels, weight, or blood pressure) and providing feedback and coaching (268–273). There are text messaging approaches that tie into a variety of different types of lifestyle and treatment programs, which vary in terms of their effectiveness (274,275). There are limited RCT data for many of these interventions, and long-term follow-up is lacking. However, for an individual with diabetes, opting into one of these programs can be helpful in providing support and, for many, is an attractive option.

Inpatient Care

Recommendations

7.33 In people with diabetes using personal CGM, the use of CGM should be continued when clinically appropriate during hospitalization, with confirmatory point-of-care glucose measurements for insulin dosing and hypoglycemia assessment and treatment under an institutional protocol. **B**

7.34 People with diabetes who are competent to safely use diabetes devices such as insulin pumps and CGM systems should be supported to continue using them in an inpatient setting or during outpatient procedures, whenever possible, and when proper supervision is available. **E**

Individuals who are comfortable using their diabetes devices, such as insulin pumps and CGM, should be allowed to use them in an inpatient setting if they are well enough to take care of the devices and have brought the necessary supplies (275–279). People with diabetes who are familiar with treating their own glucose levels can often adjust insulin doses more knowledgeably than inpatient staff who do not personally know the individual or their management style. However, this should occur based on the hospital's policies for diabetes management and use of diabetes technology, and there should be supervision to ensure that the individual is achieving and maintaining glycemic goals during acute illness in a hospitalized setting where factors, such as infection, certain medications, immobility, changes in nutrition, and others, can impact insulin sensitivity and the insulin response (280–282).

With the advent of the coronavirus disease 2019 pandemic, the FDA exercised enforcement discretion by allowing CGM device use temporarily in the hospital for patient monitoring (283). This approach has been used to reduce the use of personal protective equipment and more closely monitor patients so that health care personnel do not have to go into a patient room solely to measure a glucose level (284–286). Studies have been published assessing the effectiveness of this approach, which may ultimately lead to the approved use of CGM for monitoring hospitalized individuals (278,287–296). When used in the setting of a clinical trial or when clinical circumstances (such as during a shortage of personal protective equipment) require it, CGM can be used to manage hospitalized individuals in conjunction with BGM. Point-of-care BGM remains the approved method for glucose monitoring in hospitals, especially for dosing insulin and treating hypoglycemia. Similarly, data are emerging on the inpatient use of AID systems and their challenges (278,297,298). For more information, see Section 16, "Diabetes Care in the Hospital."

The Future

The pace of development in diabetes technology is extremely rapid. New approaches and tools are available each year. It is difficult for research to keep up with these advances because newer versions of the devices and digital solutions are already on the market by the time a study is completed. The most important component in all of these systems is the person with diabetes. Technology selection must be appropriate for the individual. Simply having a device or application does not change outcomes unless the human being engages with it to create positive health benefits. This underscores the need for the health care team to assist people with diabetes in device and program selection and to support their use through ongoing education and training. Expectations must be tempered by reality—we do not yet have technology that completely eliminates the self-care tasks necessary for managing diabetes, but the tools described in this section can make it easier to manage.

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8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: *Standards of Care in Diabetes–2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Obesity is a chronic, often relapsing disease with numerous metabolic, physical, and psychosocial complications, including a substantially increased risk for type 2 diabetes (1). There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes (2–6) and is highly beneficial in treating type 2 diabetes (7–17). In people with type 2 diabetes and overweight or obesity, modest weight loss improves glycemia and reduces the need for glucose-lowering medications (7–9), and larger weight loss substantially reduces A1C and fasting glucose and may promote sustained diabetes remission (11,18–22). Metabolic surgery, which induces on average $>$20% of body weight loss, strongly improves glycemia and often leads to remission of diabetes, improved quality of life, improved cardiovascular outcomes, and reduced mortality (23,24). Several modalities, including intensive behavioral and lifestyle counseling, obesity pharmacotherapy, and metabolic surgery, may aid in achieving and maintaining meaningful weight loss and reducing obesity-associated health risks. This section aims to provide evidence-based recommendations for obesity management, including behavioral, pharmacologic, and surgical interventions, in people with, or at high risk of, type 2 diabetes. Additional considerations regarding weight management in older individuals and children can be found in Section 13, "Older Adults," and Section 14, "Children and Adolescents," respectively.

ASSESSMENT AND MONITORING OF THE INDIVIDUAL WITH OVERWEIGHT AND OBESITY

Recommendations

8.1 Use person-centered, nonjudgmental language that fosters collaboration between individuals and health care professionals, including person-first language (e.g., "person with obesity" rather than "obese person" and "person with diabetes" rather than "diabetic person"). **E**

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*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.

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8.2a To support the diagnosis of obesity, measure height and weight to calculate BMI and perform additional measurements of body fat distribution, like waist circumference, waist-to-hip ratio, and/or waist-to-height ratio. **E**

8.2b Monitor obesity-related anthropometric measurements at least annually to inform treatment considerations. **E**

8.3 Accommodations should be made to provide privacy during anthropometric measurements. **E**

8.4 In people with type 2 diabetes and overweight or obesity, weight management should represent a primary goal of treatment along with glycemic management. **A**

8.5 People with diabetes and overweight or obesity may benefit from any magnitude of weight loss. Weight loss of 3–7% of baseline weight improves glycemia and other intermediate cardiovascular risk factors. **A** Sustained loss of >10% of body weight usually confers greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality. **B**

8.6 Individualize initial treatment approaches for obesity (i.e., lifestyle and nutritional therapy, pharmacologic agents, or metabolic surgery) **A** based on the person's medical history, life circumstances, preferences, and motivation. **C** Consider combining treatment approaches if appropriate. **E**

Obesity is defined by the World Health Organization as an abnormal or excessive fat accumulation that presents a risk to health (25). BMI (calculated as weight in kilograms divided by the square of height in meters [kg/m^2]) has been used widely to diagnose and stage obesity (overweight: BMI 25–29.9 kg/m^2; obesity class I: BMI 30–34.9 kg/m^2; obesity class II: BMI 35–39.9 kg/m^2; obesity class III: BMI ≥40 kg/m^2); however, BMI should not be relied on as a sole diagnostic and staging tool (19). Despite its ease of measurement, BMI is at most an imperfect measure of adipose tissue mass and does not measure adipose tissue distribution or function, nor does it factor in the presence of weight-related health or well-being consequences (26,27). BMI is especially prone to misclassification in individuals who are very muscular or frail, as well as in populations with different body composition and cardiometabolic risk (28). A diagnosis of obesity should be made based on an overall assessment of the individual's adipose tissue mass (BMI can be used as a general guidance), distribution (using other anthropometric measurements like waist circumference, waist-to-hip circumference ratio, or waist-to-height ratio), or function and, importantly, the presence of associated health or well-being consequences: metabolic, physical, or psychological/well-being (29).

Obesity is a key pathophysiologic driver of diabetes, other cardiovascular risk factors (e.g., hypertension, hyperlipidemia, nonalcoholic fatty liver disease, and inflammatory state), and ultimately cardiovascular and kidney disease (30). Diabetes can further exacerbate obesity, setting up a vicious cycle that contributes to disease progression and occurrence of microvascular and macrovascular complications. As such, treatment goals for both glycemia and weight are recommended in people with diabetes to address both hyperglycemia and its underlying pathophysiologic driver (obesity) and therefore benefit the person holistically.

A person-centered communication style that uses inclusive and nonjudgmental language and active listening to elicit individual preferences and beliefs and assesses potential barriers to care should be used to optimize health outcomes and health-related quality of life. Use person-first language (e.g., "person with obesity" rather than "obese person") to avoid defining people by their condition (26,31,32). Measurement of weight and height (to calculate BMI) and other anthropometric measurements should be performed at least annually to aid the diagnosis of obesity and to monitor its progression and response to treatment (33). Clinical considerations, such as the presence of comorbid heart failure or unexplained weight change, may warrant more frequent evaluation (34,35). If such measurements are questioned or declined by the individual, the practitioner should be mindful of possible prior stigmatizing experiences and query for concerns, and the value of monitoring should be explained as a part of the medical evaluation process that helps to inform treatment decisions (36,37). Accommodations should be made to ensure privacy during weighing and other anthropometric measurements, particularly for those individuals who report or exhibit a high level of disease-related distress or dissatisfaction. Anthropometric measurements should be performed and reported nonjudgmentally; such information should be regarded as sensitive health information.

Health care professionals should advise individuals with overweight or obesity and those with increasing weight trajectories that, in general, greater fat accumulation increases the risk of diabetes, cardiovascular disease, and all-cause mortality and has multiple adverse health and quality of life consequences. Health care professionals should assess readiness to engage in behavioral changes for weight loss and jointly determine behavioral and weight loss goals and individualized intervention strategies using shared decision-making (38). Strategies may include nutrition and dietary changes, physical activity and exercise, behavioral counseling, pharmacotherapy, medical devices, and metabolic surgery. The initial and subsequent therapeutic choice should be individualized based on the person's medical history, life circumstances, preferences, and motivation (39). Combination treatment approaches may be appropriate in higher-risk individuals.

Among people with type 2 diabetes and overweight or obesity who have inadequate glycemic, blood pressure, and lipid management and/or other obesity-related metabolic complications, modest and sustained weight loss (3–7% of body weight) improves glycemia, blood pressure, and lipids and may reduce the need for disease-specific medications (7–9,40). In people at risk, 3–7% weight loss reduces progression to diabetes (2,7,8,41,42). Greater weight loss may produce additional benefits (20,21). Mounting data have shown that >10% body weight loss usually confers greater benefits on glycemia and possibly diabetes remission and improves other metabolic comorbidities, including cardiovascular outcomes, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, adipose tissue inflammation, and sleep apnea, as well as physical comorbidities and quality of life (6,20,21,30,41,43–52).

With the increasing availability of more effective treatments, individuals with diabetes and overweight or obesity should be informed of the potential benefits of both modest and more substantial weight loss and guided in the range of available treatment options, as discussed in the sections below. Shared decision-making should be used when counseling on behavioral changes, intervention choices, and weight management goals.

NUTRITION, PHYSICAL ACTIVITY, AND BEHAVIORAL THERAPY

Recommendations

8.7 Nutrition, physical activity, and behavioral therapy to achieve and maintain ≥5% weight loss are recommended for people with type 2 diabetes and overweight or obesity. **B**

8.8a Interventions including high frequency of counseling (≥16 sessions in 6 months) with focus on nutrition changes, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit have been shown to be beneficial for weight loss and should be considered when available. **A**

8.8b Consider structured programs delivering behavioral counseling (face-to-face or remote) to address barriers to access. **E**

8.9 Nutrition recommendations should be individualized to the person's preferences and nutritional needs. Use nutritional plans that create an energy deficit, regardless of macronutrient composition, to achieve weight loss. **A**

8.10 When developing a plan of care, consider systemic, structural, and socioeconomic factors that may impact nutrition patterns and food choices, such as food insecurity and hunger, access to healthful food options, cultural circumstances, and other social determinants of health. **C**

8.11a For those who achieve weight loss goals, long-term (≥1 year) weight maintenance programs are recommended, when available. Effective programs provide monthly contact and support, recommend ongoing monitoring of body weight (weekly or more frequently) and other self-monitoring strategies, and encourage regular physical activity (200–300 min/week). **A**

8.11b For those who achieve weight loss goals, continue to monitor progress periodically, provide ongoing support, and recommend continuing adopted interventions to maintain goals long term. **E**

8.12 When short-term nutrition intervention using structured, very-low-calorie meals (800–1,000 kcal/day) is considered, it should be prescribed to carefully selected individuals by trained practitioners in medical settings with close monitoring. Long-term, comprehensive weight maintenance strategies and counseling should be integrated to maintain weight loss. **B**

8.13 Nutritional supplements have not been shown to be effective for weight loss and are not recommended. **A**

For a more detailed discussion of lifestyle management approaches and recommendations, see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes." For a detailed discussion of nutrition interventions, please also refer to "Nutrition Therapy for Adults With Diabetes or Pre-diabetes: A Consensus Report" (53).

Look AHEAD Trial

Although the Action for Health in Diabetes (Look AHEAD) trial did not show that the intensive lifestyle intervention reduced cardiovascular events in adults with type 2 diabetes and overweight or obesity (41), it did confirm the feasibility of achieving and maintaining long-term weight loss in people with type 2 diabetes. In the intensive lifestyle intervention group, mean weight loss was 4.7% at 8 years (42). Approximately 50% of intensive lifestyle intervention participants lost and maintained ≥5% of their initial body weight, and 27% lost and maintained ≥10% of their initial body weight at 8 years (42). Participants assigned to the intensive lifestyle group required fewer glucose-, blood pressure-, and lipid-lowering medications than those randomly assigned to standard care. Secondary analyses of the Look AHEAD trial and other large cardiovascular outcome studies document additional weight loss benefits in people with type 2 diabetes, including improved mobility, physical and sexual function, and health-related quality of life (34). Moreover, several subgroups had improved cardiovascular outcomes, including those who achieved >10% weight loss (43).

Behavioral Interventions

Significant weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit, which in most cases is approximately 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, adjusted for the individual's baseline body weight. Clinical benefits typically begin upon achieving 5% weight loss (19,54), and the benefits of weight loss are progressive; more intensive weight loss goals (>7%, >10%, >15%, etc.) may be pursued to achieve further health improvements if the individual is motivated and more intensive goals can be feasibly and safely attained.

Nutrition interventions may differ by macronutrient goals and food choices as long as they create the necessary energy deficit to promote weight loss (19,55–57). Using meal replacement plans prescribed by trained practitioners, with close monitoring, can be beneficial. Within the intensive lifestyle intervention group of the Look AHEAD trial, for example, the use of a partial meal replacement plan was associated with improvements in nutrition quality and weight loss (54), and improvement in cardiovascular risk factors (41). In a systematic review and meta-analysis, efficacy and safety of meal replacements (partial or total meal replacement) as compared with conventional diets showed improvements in A1C, FBG, body weight, and BMI (58). The nutrition choice should be based on the individual's health status and preferences, including a determination of food availability and other cultural circumstances that could affect nutrition patterns (59).

Proven intensive behavioral interventions included ≥16 sessions during an initial 6 months and focus on nutritional changes, physical activity, and behavioral strategies to achieve an ~500–750 kcal/day energy deficit. Such interventions should be provided by trained individuals and can be conducted in either individual or group sessions (54). Assessing a person's motivation level, life circumstances, and willingness to implement behavioral changes to achieve weight loss should be considered along with medical status when such interventions are recommended and initiated (38,60). If such intensive behavioral interventions are not available or accessible, structured programs delivering behavioral counseling (face-to-face or remote) can be considered; however, their effectiveness varies (61,62).

People with type 2 diabetes and overweight or obesity who have lost weight should be offered long-term (≥1 year) comprehensive weight loss maintenance programs that provide at least monthly contact with trained individuals and focus on ongoing monitoring of body weight (weekly or more frequently) and/or other self-monitoring strategies such as tracking intake, steps, etc.; continued focus on nutrition and behavioral changes; and participation in high levels of physical activity (200–300 min/week) (63,64). Some commercial and proprietary weight loss programs have shown promising weight loss results; however, results vary across these programs, most lack evidence of effectiveness, many do not satisfy guideline recommendations, and some promote unscientific and possibly dangerous practices (65,66).

Structured, very-low-calorie meals, typically 800–1,000 kcal/day, utilizing high-protein foods and meal replacement products, may increase the pace and/or magnitude of initial weight loss and glycemic improvements compared with standard behavioral interventions (20,21). However, such an intensive nutritional intervention should be provided only by trained practitioners in medical settings with close ongoing monitoring and integration with behavioral support and counseling, and only for short term (generally up to 3 months). Furthermore, due to the high risk of complications (electrolyte abnormalities, severe fatigue, cardiac arrhythmias, etc.), such intensive intervention should be prescribed only to carefully selected individuals, such as those requiring weight loss and/or glycemic management before a needed surgery, if the benefits exceed the potential risks (67–69). As weight recurrence is common, such interventions should include long-term, comprehensive weight maintenance strategies and counseling to maintain weight loss and behavioral changes (70,71).

Despite widespread marketing and exorbitant claims, there is no clear evidence that nutrition supplements (such as herbs and botanicals, high-dose vitamins and minerals, amino acids, enzymes, antioxidants, etc.) are effective for obesity management or weight loss (72–75). Several large systematic reviews show that most trials evaluating nutrition supplements for weight loss are of low quality and at high risk for bias. High-quality published studies show little or no weight loss benefits. In contrast, vitamin/mineral (e.g., iron, vitamin B12, vitamin D) supplementation may be indicated in cases of documented deficiency (76), and protein supplements may be indicated as adjuncts to medically supervised weight loss therapies (77,78).

Health disparities adversely affect people who have systematically experienced greater obstacles to health based on their race or ethnicity, socioeconomic status, gender, disability, or other factors. Overwhelming research shows that these disparities may significantly affect health outcomes, including increasing the risk for obesity, diabetes, and diabetes-related complications. Health care professionals should evaluate systemic, structural, and socioeconomic factors that may impact food choices, access to healthful foods, and nutrition patterns; behavioral patterns, such as neighborhood safety and availability of safe outdoor spaces for physical activity; environmental exposures; access to health care; social contexts; and, ultimately, diabetes risk and outcomes. For a detailed discussion of social determinants of health, refer to “Social Determinants of Health: A Scientific Review” (79).

PHARMACOTHERAPY

Recommendations

8.14 Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. **E**

8.15 When choosing glucose-lowering medications for people with type 2 diabetes and overweight or obesity, prioritize medications with beneficial effect on weight. **B**

8.16 Obesity pharmacotherapy should be considered for people with diabetes and overweight or obesity along with lifestyle changes. Potential benefits and risks must be considered. **A**

8.17 In people with diabetes and overweight or obesity, the preferred pharmacotherapy should be a glucagon-like peptide 1 receptor agonist or dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist with greater weight loss efficacy (i.e., semaglutide or tirzepatide), especially considering their added weight-independent benefits (e.g., glycemic and cardiometabolic). **A**

8.18 To prevent therapeutic inertia, for those not reaching goals, reevaluate weight management therapies and intensify treatment with additional approaches (e.g., metabolic surgery, additional pharmacologic agents, and structured lifestyle management programs). **A**

Glucose-Lowering Therapy

Numerous effective glucose-lowering medications are currently available. However, to achieve both glycemic and weight management goals for diabetes treatment, health care professionals should prioritize the use of glucose-lowering medications with a beneficial effect on weight. Agents associated with clinically meaningful weight loss include glucagon-like peptide 1 (GLP-1) receptor agonists, dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist (tirzepatide), sodium–glucose cotransporter 2 inhibitors, metformin, and amylin mimetics. Dipeptidyl peptidase 4 inhibitors, centrally acting dopamine agonist (bromocriptine), α-glucosidase inhibitors, and bile acid sequestrants (colesevelam) are considered weight neutral. In contrast, insulin secretagogues (sulfonylureas and meglitinides), thiazolidinediones, and insulin are often associated with weight gain (see Section 9, “Pharmacologic Approaches to Glycemic Treatment”).

Concomitant Medications

Health care professionals should carefully review the individual’s concomitant medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain. Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, risperidone), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin and pregabalin), β-blockers, and possibly sedating antihistamines and anticholinergics (80).

Approved Obesity Pharmacotherapy

The U.S. Food and Drug Administration (FDA) has approved several medications for weight management as adjuncts to reduced calorie diet and increased physical activity in individuals with a BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with one or more obesity-associated comorbid conditions (e.g., type 2 diabetes, hypertension, and/or dyslipidemia). Nearly all FDA-approved obesity medications have been shown to improve glycemia in people with type 2 diabetes and delay progression to type 2 diabetes in at-risk individuals (22), and some of these agents (e.g., liraglutide and semaglutide) have an indication for glucose lowering as well as weight management. Phentermine and other older adrenergic agents are approved for short-term treatment (≤12 weeks) (81), while all others are approved for long-term treatment (>12 weeks) (22) (**Table 8.1**). (Refer to Section 14, "Children and Adolescents," for medications approved for adolescents with obesity.) In addition, setmelanotide, a melanocortin 4 receptor agonist, is approved for use in cases of rare genetic mutations resulting in severe hyperphagia and extreme obesity, such as leptin receptor deficiency and proopiomelanocortin deficiency.

In people with type 2 diabetes and overweight or obesity, agents with both glucose-lowering and weight loss effects are preferred (refer to Section 9, "Pharmacologic Approaches to Diabetes Treatment"), which include agents from the GLP-1 receptor agonist class and the dual GIP and GLP-1 receptor agonist class. Should use of these medications not result in achievement of weight management goals, or if they are not tolerated or contraindicated, other obesity treatment approaches should be considered. Two phase 3 trials have demonstrated the potential for use of the dual GIP and GLP-1 receptor agonist (tirzepatide) for obesity (SURMOUNT-1, individuals with obesity, and SURMOUNT-2, individuals with obesity and type 2 diabetes) (82,83). In the SURMOUNT-2 trial, tirzepatide resulted in body weight loss of 9.6% and 11.6% more than placebo and A1C lowering of 1.55% and 1.57% more than placebo after 72 weeks of treatment with the 10 mg and 15 mg doses, respectively, with adverse effects similar to those seen with the GLP-1 receptor agonist class (83).

Health care professionals should be knowledgeable about the benefits, dosing, and risks for each treatment option to balance the potential benefits of successful weight loss against the potential risks for each individual. The high risk and prevalence of cardiovascular disease in people with diabetes has to be balanced against the lack of long-term cardiovascular outcomes trial data for agents like naltrexone-bupropion and phentermine-topiramate. All these medications are contraindicated in individuals who are pregnant or actively trying to conceive and are not recommended for use in individuals who are nursing. Individuals of childbearing potential should receive counseling regarding the use of reliable methods of contraception. Of note, while weight loss medications are often used in people with type 1 diabetes, clinical trial data in this population are limited.

Assessing Efficacy and Safety of Obesity Pharmacotherapy

Upon initiating medications for obesity, assess their efficacy and safety at least monthly for the first 3 months and at least quarterly thereafter. Modeling from published clinical trials consistently shows that early responders have improved long-term outcomes (84,85); however, it is notable that the response rate with the latest generation of obesity pharmacotherapies is much higher (48,83). Unless clinical circumstances (such as poor tolerability) or other considerations (such as financial expense or individual preference) suggest otherwise, those who achieve sufficient early weight loss upon starting a chronic obesity medication (typically defined as >5% weight loss after 3 months of use) should continue the medication long term. When early weight loss results are modest (typically <5% weight loss after 3 months of use), the benefits of ongoing treatment need to be balanced in the context of the glycemic response, the availability of other potential treatment options, treatment tolerance, and overall treatment burden.

Ongoing monitoring of the achievement and maintenance of weight management goals is recommended. For those not reaching or maintaining weight-related treatment goals, reevaluate weight management therapies and intensify treatment with additional approaches (e.g., metabolic surgery, additional pharmacologic agents, and structured lifestyle management programs).

MEDICAL DEVICES FOR WEIGHT LOSS

While gastric banding devices have fallen out of favor due to their limited long-term efficacy and high rate of complications, several minimally invasive medical devices have been approved by the FDA for short-term weight loss, including implanted gastric balloons, a vagus nerve stimulator, and gastric aspiration therapy (86). High cost, limited insurance coverage, and limited data supporting the efficacy of these devices in the treatment of individuals with diabetes has created uncertainty for their current use (87).

An oral hydrogel (cellulose and citric acid) has been approved for long-term use in those with BMI >25 kg/m^2 to simulate the space-occupying effect of implantable gastric balloons. Taken with water 30 min before meals, the hydrogel expands to fill a portion of the stomach volume to help decrease food intake during meals. The average weight loss was relatively small (2.1% greater than placebo), and very few participants had diabetes at baseline (∼10%) (88).

METABOLIC SURGERY

Recommendations

8.19 Consider metabolic surgery as a weight and glycemic management approach in people with diabetes with BMI ≥30.0 kg/m^2 (or ≥27.5 kg/m^2 in Asian American individuals) who are otherwise good surgical candidates. **A**

8.20 Metabolic surgery should be performed in high-volume centers with interprofessional teams knowledgeable about and experienced in managing obesity, diabetes, and gastrointestinal surgery (www.facs.org/quality-programs/accreditation-and-verification/metabolic-and-bariatric-surgery-accreditation-and-quality-improvement-program/). **E**

8.21 People being considered for metabolic surgery should be evaluated for comorbid psychological conditions and social and situational circumstances that have the potential to interfere with surgery outcomes. **B**

8.22 People who undergo metabolic surgery should receive long-term medical and behavioral support and routine micronutrient, nutritional, and metabolic status monitoring. **B**

8.23 If post–metabolic surgery hypoglycemia is suspected, clinical evaluation should exclude other potential disorders contributing to hypoglycemia, and management should include education, medical nutrition therapy with a registered dietitian/nutritionist experienced in post–metabolic surgery hypoglycemia, and medication treatment, as needed. **A** Continuous glucose monitoring should be considered as an important adjunct to improve safety by alerting individuals to hypoglycemia, especially

Table 8.1—Obesity pharmacotherapy

Medication name and typical adult maintenance dose	Average wholesale price (median and range for 30-day supply) (142)	National Average Drug Acquisition Cost (30-day supply) (143)	Treatment arms	Weight loss (% loss from baseline)	Common side effects (144–149)	Possible safety concerns and considerations (144–149)
Short-term treatment (12 weeks)						
Sympathomimetic amine anorectic						
Phentermine (150)						
8–37.5 mg q.d.*	$43 ($5–$90), 37.5 mg/day	$2 (37.5 mg dose)	15 mg q.d. 7.5 mg q.d. Placebo	5.0 4.9 1.9	Dry mouth, insomnia, dizziness, irritability, increased blood pressure, elevated heart rate	• Contraindicated for use in combination with monoamine oxidase inhibitors
Long-term treatment (52 or 56 weeks)						
Lipase inhibitor						
Orlistat (4)						
60 mg t.i.d. (OTC)	$52 ($41–$82)	NA	120 mg t.i.d.†	9.6	Abdominal pain, flatulence, fecal urgency	• Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants) • Rare cases of severe liver injury reported • Cholelithiasis • Nephrolithiasis
120 mg t.i.d. (Rx)	$843 ($781–$904)	$722	Placebo	5.6		
Sympathomimetic amine anorectic/antiepileptic combination						
Phentermine/topiramate ER (47)						
7.5 mg/46 mg q.d.‡	$223 (7.5 mg/46 mg dose)	$179 (7.5 mg/46 mg dose)	15 mg/92 mg q.d.§ 7.5 mg/46 mg q.d.§ Placebo	9.8 7.8 1.2	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased blood pressure	• Contraindicated for use in combination with monoamine oxidase inhibitors • Birth defects • Cognitive impairment • Acute angle-closure glaucoma
Opioid antagonist/antidepressant combination						
Naltrexone/bupropion ER (15)						
16 mg/180 mg b.i.d.	$750	$599	16 mg/180 mg b.i.d. Placebo	5.0 1.8	Constipation, nausea, headache, xerostomia, insomnia, elevated heart rate and blood pressure	• Contraindicated in people with unmanaged hypertension and/or seizure disorders • Contraindicated for use with chronic opioid therapy • Acute angle-closure glaucoma **Black box warning:** • Risk of suicidal behavior/ideation in people younger than 24 years old who have depression

Continued on p. S151

Table 8.1—Continued

Medication name and typical adult maintenance dose	Average wholesale price (median and range for 30-day supply) (142)	National Average Drug Acquisition Cost (30-day supply) (143)	Treatment arms	Weight loss (% loss from baseline)	Common side effects (144–149)	Possible safety concerns and considerations (144–149)
Glucagon-like peptide 1 receptor agonist						
Liraglutide (16,49)||						
3 mg q.d.	$1,619	$1,294	3.0 mg q.d.	6.0	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate, hypoglycemia	• Pancreatitis has been reported in clinical trials, but causality has not been established. Discontinue if pancreatitis is suspected. • Use caution in people with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury. • May cause cholelithiasis and gallstone-related complications. • Gastrointestinal disorders (severe constipation and small bowel obstruction/ileus progression) • Monitor for potential consequences of delayed absorption of oral medications. **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined
			1.8 mg q.d.	4.7		
			Placebo	2.0		
Semaglutide (48,151)||						
2.4 mg once weekly	$1,619	$1,295	2.4 mg weekly	9.6	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate, hypoglycemia	• Pancreatitis has been reported in clinical trials, but causality has not been established. Discontinue if pancreatitis is suspected. • Use caution in people with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury. • May cause cholelithiasis and gallstone-related complications. • Gastrointestinal disorders (severe constipation and small bowel obstruction/ileus progression) • Monitor for potential consequences of delayed absorption of oral medications. **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined
			1.0 mg weekly	7.0		
			Placebo	3.4		

Continued on p. S152

Table 8.1—Continued

Medication name and typical adult maintenance dose	Average wholesale price (median and range for 30-day supply) (142)	National Average Drug Acquisition Cost (30-day supply) (143)	Treatment arms	Weight loss (% loss from baseline)	Common side effects (144–149)	Possible safety concerns and considerations (144–149)
Dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist						
Tirzepatide (83)						
5 mg, 10 mg, or 15 mg once weekly	NA	NA	10 mg weekly 15 mg weekly Placebo	12.8 14.7 3.2	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate, hypoglycemia	• Pancreatitis has been reported in clinical trials, but causality has not been established. Discontinue if pancreatitis is suspected. • Use caution in people with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury. • May cause cholelithiasis and gallstone-related complications. • Gastrointestinal disorders (severe constipation and small bowel obstruction/ileus progression) • Monitor effects of oral medications with narrow therapeutic index (warfarin) or whose efficacy is dependent on threshold concentration. • Advise those using oral hormonal contraception to use or add a non-oral contraception method for 4 weeks after initiation and dose escalations. **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined.

Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; ER, extended release; OTC, over the counter; NA, data not available; Rx, prescription; t.i.d., three times daily, p.o., by mouth; SC, subcutaneous injection; AWP, average wholesale price; NADAC, National Average Drug Acquisition Cost. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. Weight loss data were extracted from the 12-week time point, as phentermine is approved for use for up to 12 weeks. †Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. ‡Maximum dose, depending on response, is 15 mg/92 mg q.d. §Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance. ||Agent has indication for reduction of cardiovascular events (49,151). AWP and NADAC prices for 30-day supply of maximum or maintenance dose as of 6 September 2023.

for those with severe hypoglycemia or hypoglycemia unawareness. **E**

8.24 In people who undergo metabolic surgery, routinely screen for psychosocial and behavioral health changes and refer to a qualified behavioral health professional as needed. **C**

8.25 Monitor individuals who have undergone metabolic surgery for insufficient weight loss or weight recurrence at least every 6–12 months. **E** In those who have insufficient weight loss or experience weight recurrence, assess for potential predisposing factors and, if appropriate, consider additional weight loss interventions (e.g., obesity pharmacotherapy). **C**

Surgical procedures for obesity treatment—often referred to interchangeably as bariatric surgery, weight loss surgery, metabolic surgery, or metabolic/bariatric surgery—can promote significant and durable weight loss and improve type 2 diabetes. Given the magnitude and rapidity of improvement of hyperglycemia and glucose homeostasis, these procedures have been suggested as treatments for type 2 diabetes even in the absence of severe obesity, hence the current preferred terminology of "metabolic surgery" (89).

A substantial body of evidence, including data from numerous large cohort studies and randomized controlled (nonblinded) clinical trials, demonstrates that metabolic surgery achieves superior glycemic management and reduction of cardiovascular risk in people with type 2 diabetes and obesity compared with nonsurgical intervention (45). In addition to improving glycemia, metabolic surgery reduces the incidence of microvascular disease (90), improves quality of life (45,91,92), decreases cancer risk, and improves cardiovascular disease risk factors and long-term cardiovascular events (93–104). Cohort studies that match surgical and nonsurgical subjects strongly suggest that metabolic surgery reduces all-cause mortality (105,106).

The overwhelming majority of procedures in the U.S. are vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). Both procedures result in an anatomically smaller stomach pouch and often robust changes in enteroendocrine hormones. In VSG, ~80% of the stomach is removed, leaving behind a long, thin sleeve-shaped pouch. RYGB creates a much smaller stomach pouch (roughly the size of a walnut), which is then attached to the distal small intestine, thereby bypassing the duodenum and jejunum.

Metabolic surgery has been demonstrated to have beneficial effects on type 2 diabetes irrespective of the presurgical BMI (107). The American Society for Metabolic and Bariatric Surgery is now recommending metabolic surgery for people with type 2 diabetes and a BMI $\geq$30 kg/m^2 (or $\geq$27.5 kg/m^2 for Asian American individuals) in surgically eligible individuals. Studies have documented diabetes remission after 1–5 years in 30–63% of individuals with RYGB (17,108).

Most notably, the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, which randomized 150 participants with poorly managed diabetes to receive either metabolic surgery or medical treatment, found that 29% of those treated with RYGB and 23% treated with VSG achieved A1C of 6.0% or lower after 5 years (45). Available data suggest an erosion of diabetes remission over time (46); at least 35–50% of individuals who initially achieve remission of diabetes eventually experience recurrence. Still, the median disease-free period among such individuals following RYGB is 8.3 years (109,110), and the majority of those who undergo surgery maintain substantial improvement of glycemia from baseline for at least 5–15 years (45,91,94,95,110–113).

Exceedingly few presurgical predictors of success have been identified, but younger age, shorter duration of diabetes (e.g., <8 years) (84), and lesser severity of diabetes (better glycemic control, not using insulin) are associated with higher rates of diabetes remission (45,94,112,114). Greater baseline visceral fat area may also predict improved postoperative outcomes, especially among Asian American people with type 2 diabetes (115).

Although surgery has been shown to improve the metabolic profiles and cardiovascular risk of people with type 1 diabetes, larger and longer-term studies are needed to determine the role of metabolic surgery in such individuals (116).

Whereas metabolic surgery has greater initial costs than nonsurgical obesity treatments, retrospective analyses and modeling studies suggest that surgery may be cost-effective or even cost-saving for individuals with type 2 diabetes. However, these results largely depend on assumptions about the long-term effectiveness and safety of the procedures (117,118).

The safety of metabolic surgery has improved significantly with continued refinement of minimally invasive (laparoscopic) approaches, enhanced training and credentialing, and involvement of interprofessional teams. Perioperative mortality rates are typically 0.1–0.5%, similar to those of common abdominal procedures such as cholecystectomy or hysterectomy (119–123). Major complications occur in 2–6% of those undergoing metabolic surgery, which compares favorably with the rates for other commonly performed elective operations (123). Postsurgical recovery times and morbidity have also dramatically declined. Minor complications and need for operative reintervention occur in up to 15% (119–128). Empirical data suggest that the proficiency of the operating surgeon and surgical team is an important factor in determining mortality, complications, reoperations, and readmissions (129). Accordingly, metabolic surgery should be performed in high-volume centers with interprofessional teams experienced in managing diabetes, obesity, and gastrointestinal surgery. Refer to the American College of Surgeons website for information on accreditation and to locate an accredited program (https://www.facs.org/quality-programs/accreditation-and-verification/metabolic-and-bariatric-surgery-accreditation-and-quality-improvement-program/).

Beyond the perioperative period, longer-term risks include vitamin and mineral deficiencies, anemia, osteoporosis, dumping syndrome, and severe hypoglycemia (130). Nutritional and micronutrient deficiencies and related complications occur with a variable frequency depending on the type of procedure and require routine monitoring of micronutrient and nutritional status and lifelong vitamin/nutritional supplementation (130). Dumping syndrome usually occurs shortly (10–30 min) after a meal and may present with diarrhea, nausea, vomiting, palpitations, and fatigue; hypoglycemia is usually not present at the time of symptoms but, in some cases, may develop several hours later. Post–metabolic surgery hypoglycemia can occur with RYGB, VSG, and other gastrointestinal procedures and may severely impact quality of life (131–133). Post–metabolic surgery hypoglycemia is driven in part by altered gastric emptying of ingested nutrients, leading to rapid intestinal glucose absorption and excessive postprandial secretion of GLP-1 and other gastrointestinal peptides. As a result, overstimulation of insulin release and a sharp drop in plasma glucose occur, most commonly 1–3 h after a high-carbohydrate meal. Symptoms range from sweating, tremor, tachycardia, and increased hunger to impaired cognition, loss of consciousness, and seizures. In contrast to dumping syndrome, which often occurs soon after surgery and improves over time, post–bariatric surgery hypoglycemia typically presents >1 year post-surgery. Diagnosis is primarily made by a thorough history, detailed records of food intake, physical activity, and symptom patterns, and exclusion of other potential causes (e.g., malnutrition, side effects of medications or supplements, dumping syndrome, and insulinoma). Initial management includes education to facilitate reduced intake of rapidly digested carbohydrates while ensuring adequate intake of protein and healthy fats, and vitamin/nutrient supplements. When available, individuals should be offered medical nutrition therapy with a dietitian experienced in post–bariatric surgery hypoglycemia and the use of continuous glucose monitoring (ideally real-time continuous glucose monitoring, which can detect dropping glucose levels before severe hypoglycemia occurs), especially for those with hypoglycemia unawareness. Medication treatment, if needed, is primarily aimed at slowing carbohydrate absorption (e.g., acarbose) or reducing GLP-1 and insulin secretion (e.g., diazoxide, octreotide) (134).

People who undergo metabolic surgery may also be at increased risk for substance abuse, worsening or new-onset depression and/or anxiety disorders, and suicidal ideation (130,135–140). Candidates for metabolic surgery should be assessed by a behavioral health professional with expertise in obesity management prior to consideration for surgery (141). Surgery should be postponed in individuals with alcohol or substance use disorders, severe depression, suicidal ideation, or other significant behavioral health conditions until these conditions have been sufficiently addressed. Individuals with preoperative or new-onset psychopathology should be assessed regularly following surgery to optimize behavioral health and postsurgical outcomes.

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9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

9.1 Treat most adults with type 1 diabetes with continuous subcutaneous insulin infusion or multiple daily doses of prandial (injected or inhaled) and basal insulin. **A**

9.2 For most adults with type 1 diabetes, insulin analogs (or inhaled insulin) are preferred over injectable human insulins to minimize hypoglycemia risk. **A**

9.3 Early use of continuous glucose monitoring is recommended for adults with type 1 diabetes to improve glycemic outcomes and quality of life and minimize hypoglycemia. **B**

9.4 Automated insulin delivery systems should be considered for all adults with type 1 diabetes. **A**

9.5 To improve glycemic outcomes and quality of life and minimize hypoglycemia risk, most adults with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake and, additionally, to fat and protein intake. They should also be taught how to modify the insulin dose (correction dose) based on concurrent glycemia, glycemic trends (if available), sick-day management, and anticipated physical activity. **B**

9.6 Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not require reconstitution are preferred. **E**

9.7 Insulin treatment plan and insulin-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted to incorporate specific

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*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.

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factors that impact choice of treatment and ensure achievement of individualized glycemic goals. **E**

Insulin Therapy

Insulin treatment is essential for individuals with type 1 diabetes because the hallmark of type 1 diabetes is absent or near-absent β-cell function. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily injections for the six or seven decades after the discovery of insulin. Over the past four decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3). The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive control (7%) led to $\sim$50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-years of therapy) (1). Follow-up of participants from the DCCT demonstrated fewer macrovascular and microvascular complications in the group that received intensive treatment. Achieving intensive glycemic goals during the active treatment period of the study had a beneficial impact over the 20 years after the active treatment component of the study ended (1–3).

Insulin replacement plans typically consist of basal insulin, mealtime insulin, and correction insulin (4). Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant and consistent plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with injectable human insulins (5–7). More recently, two injectable ultra-rapid-acting analog (URAA) insulin formulations were developed to accelerate absorption and provide more activity in the first portion of their profile compared with the other RAA (8,9). Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA (10) (see also subsection ALTERNATIVE INSULIN ROUTES in PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES). These newer formulations may cause less hypoglycemia, while improving postprandial glucose excursions and administration flexibility (in relation to prandial intake), compared with RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14).

Despite the advantages of insulin analogs in individuals with type 1 diabetes, the expense and/or intensity of treatment required for their use may be prohibitive. There are multiple approaches to insulin treatment. The central precept in the management of type 1 diabetes is that some form of insulin be given in a defined treatment plan tailored to the individual to prevent diabetic ketoacidosis (DKA) and minimize clinically relevant hypoglycemia while achieving the individual's glycemic goals. The impact of the introduction of interchangeable biosimilars and unbranded versions of some analog products as well as current and upcoming price reductions on insulin access need to be evaluated. Reassessment of insulin-taking behavior and adjustment of treatment plans to account for specific factors, including cost, that impact choice of treatment is recommended at regular intervals (every 3–6 months).

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. A systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (-0.30% [95% CI -0.58 to -0.02]) and for reducing severe hypoglycemia rates in children and adults (15). Use of CSII is associated with improvement in quality of life, particularly in areas related to fear of hypoglycemia and diabetes distress, compared with multiple daily injections of insulin (16,17). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (4). Integration of continuous glucose monitoring (CGM) into the treatment plan soon after diagnosis improves glycemic outcomes, decreases hypoglycemic events, and improves quality of life for individuals with type 1 diabetes (18–23). Its use is now considered standard of care for most people with type 1 diabetes (4) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level, with further improvements when using devices with predictive low glucose insulin delivery suspension (24,25).

Automated insulin delivery (AID) systems are safe and effective for people with type 1 diabetes. Randomized controlled trials and real-world studies have demonstrated the ability of commercially available systems to improve achievement of glycemic goals while reducing the risk of hypoglycemia (26–31). Data are emerging on the safety and effectiveness of do-it-yourself systems (32,33). Evidence suggests that an AID hybrid closed-loop system is superior to AID sensor-augmented pump therapy for increased percentage of time in range and reduction of hypoglycemia (34,35).

Intensive insulin management using a version of CSII and CGM should be considered in individuals with type 1 diabetes whenever feasible. AID systems are preferred and should be considered for individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) to improve time in range and reduce A1C and hypoglycemia (26,28–31,36–42). When choosing among insulin delivery systems, individual preferences, cost, insulin type, dosing plan, and self-management capabilities should be considered. See Section 7, "Diabetes Technology," for a full discussion of insulin delivery devices.

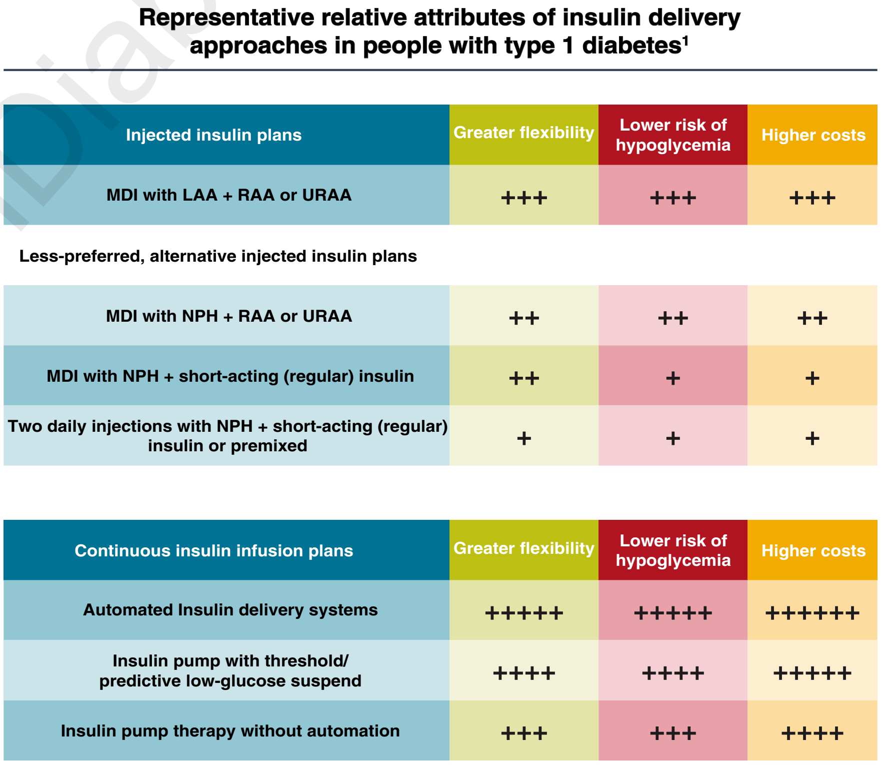
In general, individuals with type 1 diabetes require approximately 30–50% of their daily insulin as basal and the remainder as prandial (43). This proportion is dependent on a number of factors, including but not limited to carbohydrate consumption, age, pregnancy status, and puberty stage (4,44–48). Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts may be required during puberty, menses, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in adults with type 1 diabetes who are metabolically stable, with approximately one-half administered as prandial insulin given to manage blood glucose after meals and the remaining portion as basal insulin to manage glycemia in the periods between meal absorption (49). Starting doses and those soon after diagnosis may be higher, if an individual presents with ketoacidosis, or lower (0.2–0.6 units/kg), particularly in young children and those with continued endogenous insulin production (during the partial remission phase or “honeymoon period,” or in people who present with type 1 diabetes in adulthood) (49–52). This guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement “Type 1 Diabetes Management Through the Life Span” provides a thorough overview of type 1 diabetes treatment (53).

Typical multidose treatment plans for individuals with type 1 diabetes combine premeal use of prandial insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best managed by a well-timed injection or inhalation of prandial insulin. Prandial insulin should ideally be administered prior to meal consumption; however, the optimal time to administer varies based on the pharmacokinetics of the formulation (regular, RAA, or inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demands for glucose. To approach this variability in people using insulin treatment, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education on how to adjust prandial insulin to account for nutritional intake and the correction dose based on premeal glucose levels, anticipated activity, and sick-day management can be effective and should be offered to most individuals (54–59). Education regarding adjustment of prandial insulin dose for glycemic trends should be provided to individuals who are using CGM alone or an AID system (60–63). Further adjustment of prandial insulin doses for nutritional intake of protein and fat, in addition to carbohydrates, is recommended but may be more feasible for individuals using CSII than for those using multiple daily injections (56). With some AID systems, use of a simplified meal announcement method may be an alternative for prandial insulin dosing (31,64) (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” and Section 7, “Diabetes Technology”).

Due to the risk of hypoglycemia with insulin treatment, all individuals with type 1 diabetes should be prescribed glucagon. Individuals with type 1 diabetes and/or those in close contact with individuals with type 1 diabetes should be educated on the use and administration of the individual’s prescribed glucagon product. The glucagon product available to individuals may differ based on coverage and cost, however those that do not require reconstitution are preferred for ease of administration (65,66). Clinicians should routinely review the individual’s access to glucagon, as appropriate glucagon prescribing is low (67,68). See Section 6, “Glycemic Goals and Hypoglycemia,” for additional information on hypoglycemia and glucagon in individuals with diabetes. The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin plans and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (4).

Insulin Administration Technique

Ensuring that individuals and/or caregivers understand correct insulin administration technique is important to optimize glycemic management and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the correct way. Recommendations have been published elsewhere outlining best practices



Representative relative attributes of insulin delivery approaches in people with type 1 diabetes^1

Injected insulin plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin plans			
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

Continuous insulin infusion plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
Automated Insulin delivery systems	+++++	+++++	++++++
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	+++++
Insulin pump therapy without automation	+++	+++	++++

Figure 9.1—Choices of insulin plans in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. ^{1}The number of plus signs (+) is an estimate of relative association of the plan with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered plans. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Adapted from Holt et al. (4).

for insulin administration (69). Proper insulin administration technique includes injection or infusion (for CSII or AID systems) into appropriate body areas, injection or infusion site rotation, appropriate care of injection or infusion sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery. Selection of method of administration (vial and syringe, insulin pen, connected insulin pens/devices, or insulin pumps) will depend on a variety of individual-specific factors and needs, cost and coverage, and individual preferences. Reassessment of the appropriate administration technique via whichever method is used should be completed during routine follow-up.

Exogenously delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin administration include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity (70).

Injection or infusion site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection or infusion site rotation and how to recognize and avoid areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of administration device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection or infusion technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering medications have been studied for their efficacy as adjunct to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (∼1 kg) with pramlintide (71). Similar results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes was associated with small reductions in body weight, insulin dose, and lipid levels but did not sustainably improve A1C (72,73). The largest clinical trials of glucagon-like

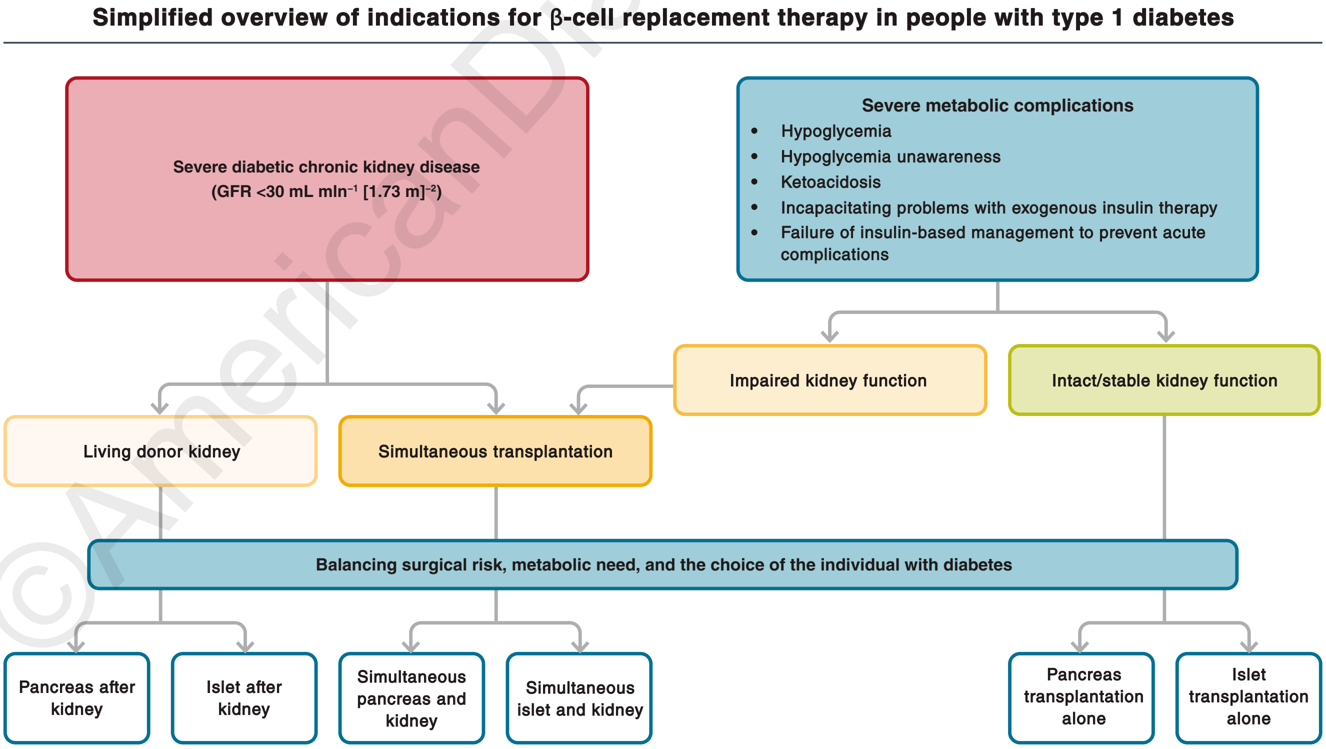

Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes
Severe diabetic chronic kidney disease (GFR <30 mL mln⁻¹ [1.73 m]⁻²)
Severe metabolic complications
Hypoglycemia
Hypoglycemia unawareness
Ketoacidosis
Incapacitating problems with exogenous insulin therapy
Failure of insulin-based management to prevent acute complications
Impaired kidney function
Intact/stable kidney function
Living donor kidney
Simultaneous transplantation
Balancing surgical risk, metabolic need, and the choice of the individual with diabetes
Pancreas after kidney
Islet after kidney
Simultaneous pancreas and kidney
Simultaneous islet and kidney
Pancreas transplantation alone
Islet transplantation alone

Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation or islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the individual has end-stage renal disease, which may be performed simultaneously or after kidney transplantation. All decisions about transplantation must balance the surgical risk, metabolic need, and the choice of the individual with diabetes. GFR, glomerular filtration rate. Reprinted from Holt et al. (4).

Table 9.1—Examples of subcutaneous insulin treatment plans

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Plans that more closely mimic normal insulin secretion				
Insulin pump therapy (also including AID systems: hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 30–50% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with premeal insulin ∼15 min before eating.	Can adjust basal rates for varying insulin sensitivity by time of day, for exercise, and for sick days. Flexibility in meal timing and content. Pump can deliver insulin in increments of fractions of units. Potential for integration with CGM for AID systems. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive plan. Must continuously wear one or more devices. Risk of rapid development of ketosis or DKA with interruption of insulin delivery. Potential reactions to adhesives and site infections. Most technically complex approach (harder for people with lower numeracy or literacy skills).	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. Basal rates: adjust based on overnight, fasting or daytime glucose outside of activity of URAA/RAA bolus.
MDI: LAA + flexible doses of URAA or RAA at meals	LAA once daily (insulin detemir or insulin glargine may require twice-daily dosing); generally 30–50% of TDD. Mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose.	Can use pens for all components. Flexibility in meal timing and content. Insulin analogs cause less hypoglycemia than human insulins.	At least four daily injections. Most costly insulins. Smallest increment of insulin is 1 unit (0.5 unit with some pens). LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. LAA: based on overnight or fasting glucose or daytime glucose outside of activity time course, or URAA or RAA injections.
MDI plans with less flexibility				
Four injections daily with fixed doses of N and RAA	Pre-breakfast: RAA ∼20% of TDD. Pre-lunch: RAA ∼10% of TDD. Pre-dinner: RAA ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

Continued on p. S163

Table 9.1—Continued

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Four injections daily with fixed doses of N and R	Pre-breakfast: R ∼20% of TDD. Pre-lunch: R ∼10% of TDD. Pre-dinner: R ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. R can be dosed based on ICR and correction. All meals have R coverage. Least expensive insulins.	Greater risk of nocturnal hypoglycemia with N. Greater risk of delayed post-meal hypoglycemia with R. Requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.	Pre-breakfast R: based on BGM after breakfast or before lunch. Pre-lunch R: based on BGM after lunch or before dinner. Pre-dinner R: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.
Plans with fewer daily injections				
Three injections daily: N + R or N + RAA	Pre-breakfast: N ∼ 40% TDD + R or RAA ∼15% TDD. Pre-dinner: R or RAA ∼15% TDD. Bedtime: N ∼ 30% TDD.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injection in middle of day. Morning N covers lunch to some extent. Same advantages of RAAs over R. Least (N + R) or less expensive insulins than MDI with analogs.	Greater risk of nocturnal hypoglycemia with N than LAAs. Greater risk of delayed post-meal hypoglycemia with R than RAAs. Requires relatively consistent mealtimes and carbohydrate intake. Coverage of post-lunch glucose often suboptimal. R must be injected at least 30 min before meal for better effect.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Pre-dinner R: based on bedtime BGM. Pre-dinner RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.
Twice-daily "split-mixed": N + R or N + RAA	Pre-breakfast: N ∼ 40% TDD + R or RAA ∼15% TDD. Pre-dinner: N ∼ 30% TDD + R or RAA ∼15% TDD.	Least number of injections for people with strong preference for this. Insulins can be mixed in one syringe. Least (N + R) or less (N + RAA) expensive insulins vs. analogs. Eliminates need for doses during the day.	Risk of hypoglycemia in afternoon or middle of night from N. Fixed mealtimes and meal content. Coverage of post-lunch glucose often suboptimal. Difficult to reach targets for blood glucose without hypoglycemia.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Evening R: based on bedtime BGM. Evening RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.

AID, automated insulin delivery; BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; LAA, long-acting analog; MDI, multiple daily injections; N, NPH insulin; R, short-acting (regular) insulin; RAA, rapid-acting analog; TBR, time below range; TDD, total daily insulin dose; TIR, time in range; URAA, ultra-rapid-acting analog. Adapted from Holt et al. (4).

peptide 1 receptor agonists (GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, and results showed modest A1C reductions (∼0.4%), decreases in weight (∼5 kg), and reductions in insulin doses (74,75). Similarly, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C, reduced body weight, and improved blood pressure (76); however, SGLT2 inhibitor use in type 1 diabetes was associated with an increased rate of DKA. The SGLT1/2 inhibitor sotagliflozin has been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C and body weight (77); however, sotagliflozin use was associated with an eightfold increase in DKA compared with placebo (78). The studies that led to the approved indication for heart failure (HF) excluded individuals with type 1 diabetes or a history of DKA (79,80). See section PREVENTION AND TREATMENT OF HEART FAILURE within Section 10, "Cardiovascular Disease and Risk Management," for information on risk mitigation with the use of SGLT inhibitors in those with type 1 diabetes. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on patient selection and precautions (81).

There are currently no approved therapies for preservation of C-peptide or delaying the progression of clinical type 1 diabetes. Higher C-peptide levels have been associated with better A1C, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia (82). Several therapies, including verapamil and monoclonal antibodies, are currently under active investigation.

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous kidney transplantation, following kidney transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (83). In much of the world, allogenic islet transplantation is regulated as an organ transplant. However, in the U.S., allogenic islet transplantation is regulated as a cell therapy, and the first such allogeneic islet cell therapy, donislecel-jujn, was approved in 2023. Donislecel is indicated for the treatment of adults with type 1 diabetes who are unable to approach their A1C goal because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

The 2021 ADA/EASD consensus report on the management of type 1 diabetes in adults offers a simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes (**Fig. 9.2**) (4).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.8 Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of therapeutic inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. **A**

9.9 A person-centered shared decision-making approach should guide the choice of pharmacologic agents for adults with type 2 diabetes. Consider the effects on cardiovascular and renal comorbidities; effectiveness; hypoglycemia risk; impact on weight, cost and access; risk for adverse reactions and tolerability; and individual preferences (**Fig. 9.3** and **Table 9.2**). **E**

9.10 The glucose-lowering treatment plan should consider approaches that support weight management goals (**Fig. 9.3** and **Table 9.2**) for adults with type 2 diabetes. **A**

9.11 For adults with type 2 diabetes, use pharmacological strategies that provide sufficient effectiveness to achieve and maintain the intended treatment goals. **A**

9.12 Treatment modification (intensification or deintensification) for adults not meeting individualized treatment goals should not be delayed. **A**

9.13 Medication plan and medication-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.2**). **E**

9.14 Early combination therapy can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals. **A**

9.15 In adults with type 2 diabetes without cardiovascular and/or kidney disease, pharmacologic agents should address both the individualized glycemic and weight goals (**Fig. 9.3**). **A**

9.16 In adults with type 2 diabetes who have not achieved their individualized glycemic goals, selection of subsequent glucose-lowering agents should take into consideration the individualized glycemic and weight goals as well as the presence of other metabolic comorbidities and the risk of hypoglycemia. **A**

9.17 In adults with type 2 diabetes who have not achieved their individualized weight goals, additional weight management interventions (e.g., intensification of lifestyle modifications, structured weight management programs, pharmacologic agents, or metabolic surgery, as appropriate) are recommended. **A**

9.18 In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure (HF), and/or chronic kidney disease (CKD), the treatment plan should include agent(s) that reduce cardiovascular and kidney disease risk (e.g., sodium–glucose cotransporter 2 inhibitor [SGLT2] and/or glucagon-like peptide 1 receptor agonist [GLP-1 RA]) (**Fig. 9.3**, **Table 9.2**, **Table 10.3*B***, and **Table 10.3*C***) for glycemic management and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors (**Fig. 9.3**) (see Section 10, "Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

9.19 In adults with type 2 diabetes who have HF (with either reduced or preserved ejection fraction), an SGLT2 inhibitor is recommended, for glycemic management and prevention of HF hospitalizations (see Section 10, "Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

9.20 In adults with type 2 diabetes who have CKD (with confirmed estimated glomerular filtration rate [eGFR] of 20–60 mL/min per 1.73 m^2 and/or albuminuria), an SGLT2 inhibitor should be used for minimizing progression of CKD, reduction in cardiovascular events, and reduction in hospitalizations for HF (**Fig. 9.3**); however, the glycemic benefits of SGLT2 inhibitors are reduced at eGFR $<$45 mL/min per 1.73 m^2 (see Section 11, "Chronic Kidney Disease and Risk Management" for details on renal risk reduction recommendations). **A**

9.21 In adults with type 2 diabetes and advanced CKD (eGFR $<$30 mL/min per 1.73 m^2), a GLP-1 RA is preferred for glycemic management due to lower risk of hypoglycemia and for cardiovascular event reduction. **B**

9.22 In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if there is evidence of ongoing catabolism (e.g., unexpected weight loss), if symptoms of hyperglycemia are present, or when A1C or blood glucose levels are very high (i.e., A1C $>$10% [$>$86 mmol/mol] or blood glucose $\geq$300 mg/dL [$\geq$16.7 mmol/L]). **E**

9.23 In adults with type 2 diabetes, a GLP-1 RA, including a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, is preferred to insulin (**Fig. 9.4**). **A**

9.24 If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. **A**

9.25 In adults with type 2 diabetes, glucose-lowering agents may be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (i.e., weight, cardiometabolic, or kidney benefits). **A**

9.26 To minimize the risk of hypoglycemia and treatment burden when starting insulin therapy in adults with type 2 diabetes, reassess the need for and/or dose of glucose-lowering agents with higher hypoglycemia risk (i.e., sulfonylureas and meglitinides). **A**

9.27 Monitor for signs of overbasalization during insulin therapy, such as basal dose exceeding $\sim$0.5 units/kg/day, significant bedtime-to-morning or postprandial-to-preprandial glucose differential, occurrences of hypoglycemia (aware or unaware), and high glycemic variability. When overbasalization is suspected, a thorough reevaluation should occur promptly to further tailor therapy to the individual's needs. **E**

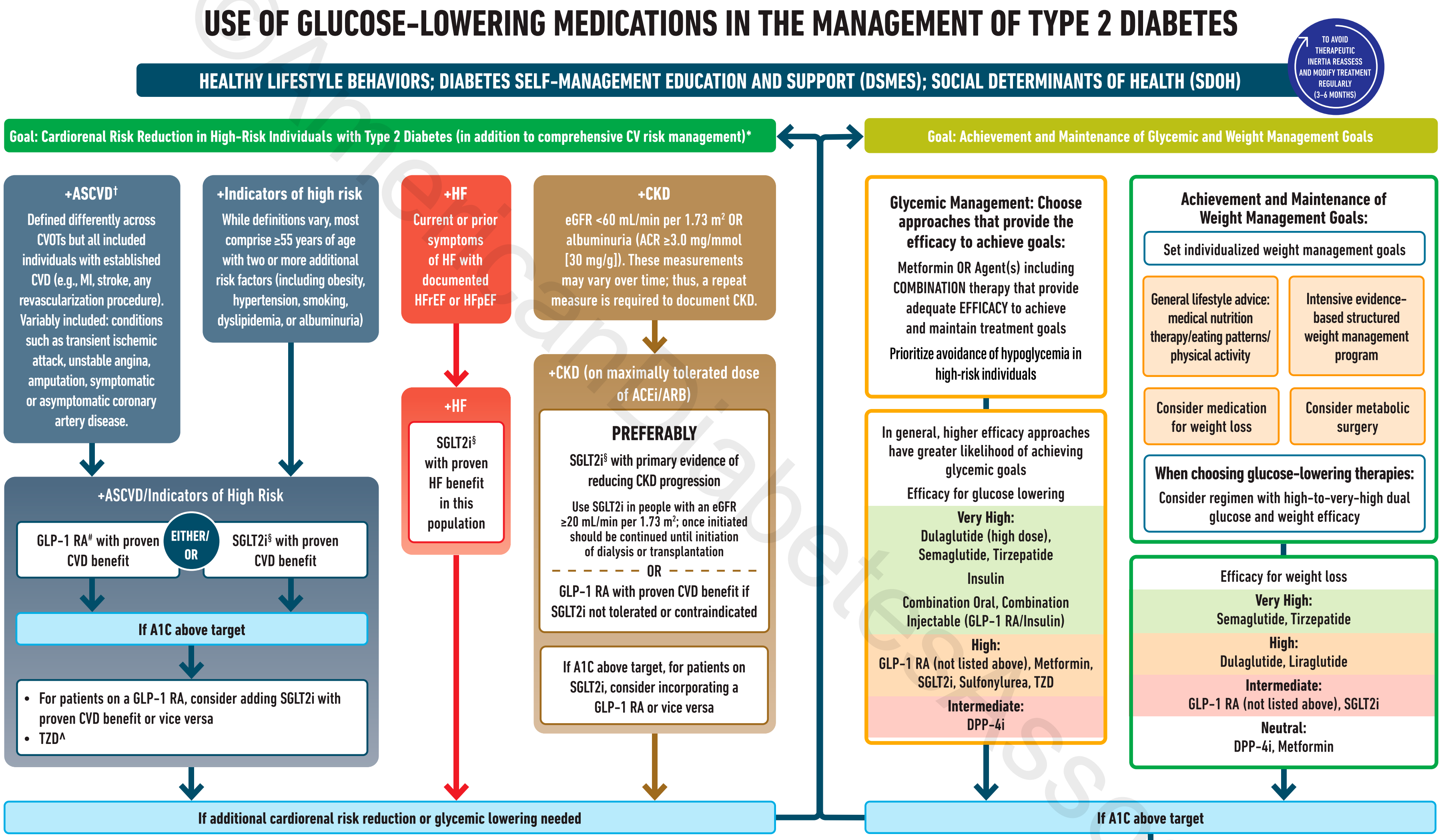
9.28 Routinely assess all people with diabetes for financial obstacles that could impede their diabetes management. Clinicians, members of the diabetes care team, and social services professionals should work collaboratively, as appropriate and feasible, to support these individuals by implementing strategies to reduce costs, thereby improving their access to evidence-based care. **E**

9.29 In adults with diabetes and cost-related barriers, consider use of lower-cost medications for glycemic management (i.e., metformin, sulfonylureas, thiazolidinediones, and human insulin) within the context of their risks for hypoglycemia, weight gain, cardiovascular and kidney events, and other adverse effects. **E**

The ADA/EASD consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2022" (84) recommends a holistic, multifaceted, person-centered approach accounting for the complexity of managing type 2 diabetes and its complications across the life span. Person-specific factors that affect choice of treatment include individualized glycemic goals (see Section 6, "Glycemic Goals and Hypoglycemia"), individualized weight goals, the individual's risk for hypoglycemia, and the individual's history of or risk factors for cardiovascular, kidney, liver, and other comorbidities and complications of diabetes (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," Section 10, "Cardiovascular Disease and Risk Management," and Section 11 "Chronic Kidney Disease and Risk Management"). In addition, treatment decisions must consider the tolerability and side effect profiles of medications, complexity of the medication plan and the individual's capacity to implement it given their specific situation and context, and the access, cost, and availability of medication. Lifestyle modifications and health behaviors that improve health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") should be emphasized along with any pharmacologic therapy. Section 13, "Older Adults," and Section 14, "Children and Adolescents," have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management," have recommendations for the use of glucose-lowering drugs in the management of cardiovascular disease and kidney disease, respectively.

Choice of Glucose-Lowering Therapy

Healthy lifestyle behaviors, diabetes self-management, education, and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals and preferences. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are contraindications. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (84). In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD), the treatment plan should include agents that reduce cardiovascular and kidney disease risk (see **Fig. 9.3**, **Table 9.2**, Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and semaglutide, the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA tirzepatide, insulin, combination



USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk
GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF
SGLT2i§ with proven HF benefit in this population

+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering
Very High: Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High: GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate: DPP-4i

Achievement and Maintenance of Weight Management Goals:
Set individualized weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/physical activity
Intensive evidence-based structured weight management program
Consider medication for weight loss
Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss
Very High: Semaglutide, Tirzepatide
High: Dulaglutide, Liraglutide
Intermediate: GLP-1 RA (not listed above), SGLT2i
Neutral: DPP-4i, Metformin

If A1C above target

Identify barriers to goals:
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (84).

Table 9.2—Medications for lowering glucose, summary of characteristics

		Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
					Effect on MACE	HF	Progression of DKD	Dosing/use considerations*			
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors		Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs		High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Counsel patients about potential for ileus (semaglutide SQ) • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
Dual GIP and GLP-1 RA		Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Not recommended for individuals with history of gastroparesis • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia
Insulin	**Human**	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs								SQ	High	

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NASH, nonalcoholic steatohepatitis; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (104). [2]Tsapas et al. (152). Adapted from Davies et al. (84).

oral therapy, and combination injectable therapy. Weight management is a distinct treatment goal, along with glycemic management, in individuals with type 2 diabetes, as it has multifaceted benefits, including improved glycemic management, reduction in hepatic steatosis, and improvement in cardiovascular risk factors (84–86). The glucose-lowering treatment plan should therefore consider approaches that support weight management goals, with semaglutide and tirzepatide currently having the highest weight loss efficacy among agents approved for glycemic management (**Fig. 9.3** and **Table 9.2**) (84,87,88). Additional weight management approaches, alone or in combination, should be used if needed to achieve individual goals (i.e., intensive behavioral management programs, weight loss pharmacotherapies, or metabolic surgery). See Section 8, "Obesity and Weight Management," for approaches to achieve weight management goals.

Metformin is effective and safe, is inexpensive and widely available, and may reduce risk of cardiovascular events and death (89). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, is weight neutral, does not cause hypoglycemia, and reduces cardiovascular mortality (90).

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration and/or using extended-release formulation. The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be safely used in people with estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 (91). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (92). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 levels (93) (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities") in individuals treated with metformin for an extended period of time.

When A1C is $\geq$1.5% above the individualized glycemic goal (see Section 6, "Glycemic Goals and Hypoglycemia," for appropriate goals), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their goal A1C level (84,94) (**Fig. 9.3** and **Table 9.2**). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination medication plan when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels $\geq$300 mg/dL ($\geq$16.7 mmol/L) or A1C $>$10% ($>$86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (unexpected weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the medication plan and/or changing to noninsulin agents is often possible. However, there is evidence that people with poorly managed hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea, GLP-1 RA, or dual GIP and GLP-1 RA (87,88,95). GLP-1 RAs and tirzepatide have additional benefits over insulin and sulfonylureas, specifically lower risk for hypoglycemia (both) and favorable weight (both), cardiovascular (GLP-1 RAs), and kidney (GLP-1 RAs) end points.

Combination Therapy

Because type 2 diabetes is a progressive disease in many individuals, maintenance of glycemic goals often requires combination therapy. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain goal A1C. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and reduce potential side effects and expense (96). However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (97,98) and later combination therapy for longer durability of glycemic effect (99). The VERIFY (Vildagliptin Efficacy in combination with metformin For earlY treatment of type 2 diabetes) trial demonstrated that initial combination therapy—in this case of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin—is superior to sequential addition of medications for extending primary and secondary failure (100). Initial combination therapy should be considered in people presenting with A1C levels 1.5–2.0% above goal. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular and kidney disease risk reduction (e.g., GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors) may allow for weaning of the current medication plan, particularly of agents that may increase the risk of hypoglycemia and weight gain. Thus, treatment intensification may not necessarily follow a pure sequential addition of therapy but instead reflect a tailoring of the medication plan in alignment with person-centered treatment goals and pursuit of multifaceted treatment goals (**Fig. 9.3**).

Treatment intensification, deintensification, or modification—as appropriate—for people not meeting individualized treatment goals should not be delayed. Shared decision-making is important in discussions regarding treatment change. The choice of medication added to initial therapy is based on the clinical characteristics of the individual and their preferences and goals for care. Important clinical characteristics include the presence of overweight or obesity, established ASCVD or indicators of high ASCVD risk, HF, CKD, obesity, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, hypoglycemia, and risk for specific adverse drug effects, as well as safety, tolerability, accessibility, usability, and cost. Results from comparative effectiveness meta-analyses suggest that each new class of oral noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (8–11 mmol/mol); if a GLP-1 RA or the dual GIP and GLP-1 RA is added, a 1 to $\geq$2% lowering in A1C is expected (87,101,102) (**Fig. 9.3** and **Table 9.2**).

For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated cardiovascular benefit (see **Table 9.2**, **Table 10.3*B***, and **Table 10.3*C***) is recommended as part of the glucose-lowering plan independent of A1C, independent of metformin use, and in consideration of person-specific factors (**Fig. 9.3**). Individuals with these comorbidities already achieving their individualized glycemic goals with other medications may benefit from switching to these preferred medications, if possible, to reduce risk of ASCVD, HF, and/or CKD in addition to achieving glycemic goals (see Section 10, “Cardiovascular Disease and Risk Management” and Section 11, “Chronic Kidney Disease and Risk Management”). This is particularly important as SGLT2 inhibitors and GLP-1 RA are associated with lower risk of hypoglycemia and individuals with ASCVD, HF, and CKD experience heightened hypoglycemia risk.

For people without established ASCVD, indicators of high ASCVD risk, HF, or CKD, medication choice is guided by efficacy in support of individualized glycemic and weight management goals, avoidance of side effects (particularly hypoglycemia and weight gain), cost/access, and individual preferences (103). A systematic review and network meta-analysis suggests that the greatest reductions in A1C level are with insulin plans, specific GLP-1 RAs (particularly semaglutide), and tirzepatide (87,88,104). In all cases, treatment plans need to be continuously reviewed for efficacy, side effects, and burden (**Table 9.2**). In some instances, the individual will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, hypoglycemia, intolerable side effects, new contraindications, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). Section 13, “Older Adults,” has a full discussion of treatment considerations in older adults, in whom changes of glycemic goals and de-escalation of therapy are common.

The need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent medication plans is a well-established approach that is effective for many individuals. In addition, evidence supports the utility of GLP-1 RAs in people not attaining their glycemic goals. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is commercially available (105). In trials comparing the addition of an injectable GLP-1 RA, dual GIP and GLP-1 RA, or insulin in people needing further glucose lowering, glycemic efficacies of injectable GLP-1 RA and dual GIP and GLP-1 RA were similar to or greater than that of basal insulin (106–113). GLP-1 RAs and dual GIP and GLP-1 RA in these trials had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support high potency GLP-1 RAs and dual GIP and GLP-1 RA as the preferred options for individuals requiring the potency of an injectable therapy for glucose management (**Fig. 9.4**). In individuals who are intensified to insulin therapy, combination therapy with a GLP-1 RA or a dual GIP and GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effect, as well as weight and hypoglycemia benefit, than treatment intensification with insulin alone (84,114). However, cost and tolerability issues are important considerations in GLP-1 RA and dual GIP and GLP-1 RA use.

Costs for diabetes medications have increased dramatically over the past two decades, and an increasing proportion is now passed on to people with diabetes and their families (115). **Table 9.3** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (116) and National Average Drug Acquisition Costs (NADAC) (117), separate measures to allow for a comparison of drug prices, but do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the individual. Medication costs can be a major source of stress for people with diabetes and contribute to worse medication-taking behavior (118); cost-reducing strategies may improve medication-taking behavior in some cases (119). Although caps on costs are starting to occur for insulin products, no such caps exist for diabetes durable medical equipment or for noninsulin medications. It is therefore essential to screen all people with diabetes for financial concerns and cost-related barriers to care and to engage members of the health care team—including pharmacists, certified diabetes care and education specialists, social workers, community health workers, community paramedics, and others—to identify cost-saving opportunities for medications, diabetes durable medical equipment, and glucagon (120).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in adults with type 2 diabetes treated with an SGLT2 inhibitor or GLP-1 RA; see Section 10, “Cardiovascular Disease and Risk Management,” for details. Participants enrolled in many of the cardiovascular outcomes trials had A1C $\geq$6.5% ($\geq$48 mmol/mol), with more than 70% taking metformin at baseline, with analyses indicating benefit with or without metformin (84). Thus, a practical extension of these results to clinical practice is to use these medications preferentially in people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these individuals, incorporating one of the SGLT2 inhibitors and/or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (see **Fig. 9.3**, **Table 9.2**, and Section 10, “Cardiovascular Disease and Risk Management”). Emerging data suggest that use of both classes of drugs will provide additional cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 RA may be considered to provide the complementary outcomes benefits associated with these classes of medication (121). In cardiovascular outcomes trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, and dulaglutide all had beneficial effects on indices of CKD, while dedicated renal outcomes studies have demonstrated benefit of specific SGLT2 inhibitors. See Section 11, “Chronic Kidney Disease and Risk Management,” for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Individuals at low risk for ASCVD may benefit from GLP-1 RA therapy to reduce their risk of future ASCVD events, although the evidence is currently limited. The Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study (GRADE), which was designed to examine the comparative effectiveness of insulin glargine U-100, glimepiride, liraglutide, and sitagliptin in individuals with short duration of diabetes with respect to achieving and maintaining glycemic control, found that individuals treated with liraglutide had a slightly lower risk of cardiovascular disease compared with individuals receiving the other three treatments (hazard ratio 0.7 [95% CI 0.6–0.9]), although no significant differences were found for major adverse cardiovascular events, hospitalization for HF, or cardiovascular death (122).

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See the section INSULIN ADMINISTRATION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to individuals with diabetes, and clinicians should avoid using insulin as a threat or describing it as a sign of personal failure or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents should be emphasized. Educating and involving people with diabetes in insulin management is beneficial. For example, instruction of individuals with type 2 diabetes initiating insulin in self-titration of insulin doses based on glucose monitoring improves glycemic management (123). Comprehensive education regarding blood glucose monitoring, nutrition, and the avoidance and appropriate treatment of hypoglycemia are critically important in any individual using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to metformin and other noninsulin injectables for individuals with type 2 diabetes. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (124,125). Attainment of fasting glucose goals can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine or detemir) have been demonstrated to reduce the risk of level 2 hypoglycemia and nocturnal hypoglycemia compared with NPH insulin (126). Longer-acting basal analogs (U-300 glargine or degludec) convey a lower nocturnal hypoglycemia risk compared with U-100 glargine (127,128). Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than ∼0.5 units/kg, high bedtime-to-morning or preprandial-to-postprandial glucose differential (e.g., bedtime-to-morning glucose differential ≥50 mg/dL [≥2.8 mmol/L]), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (129).

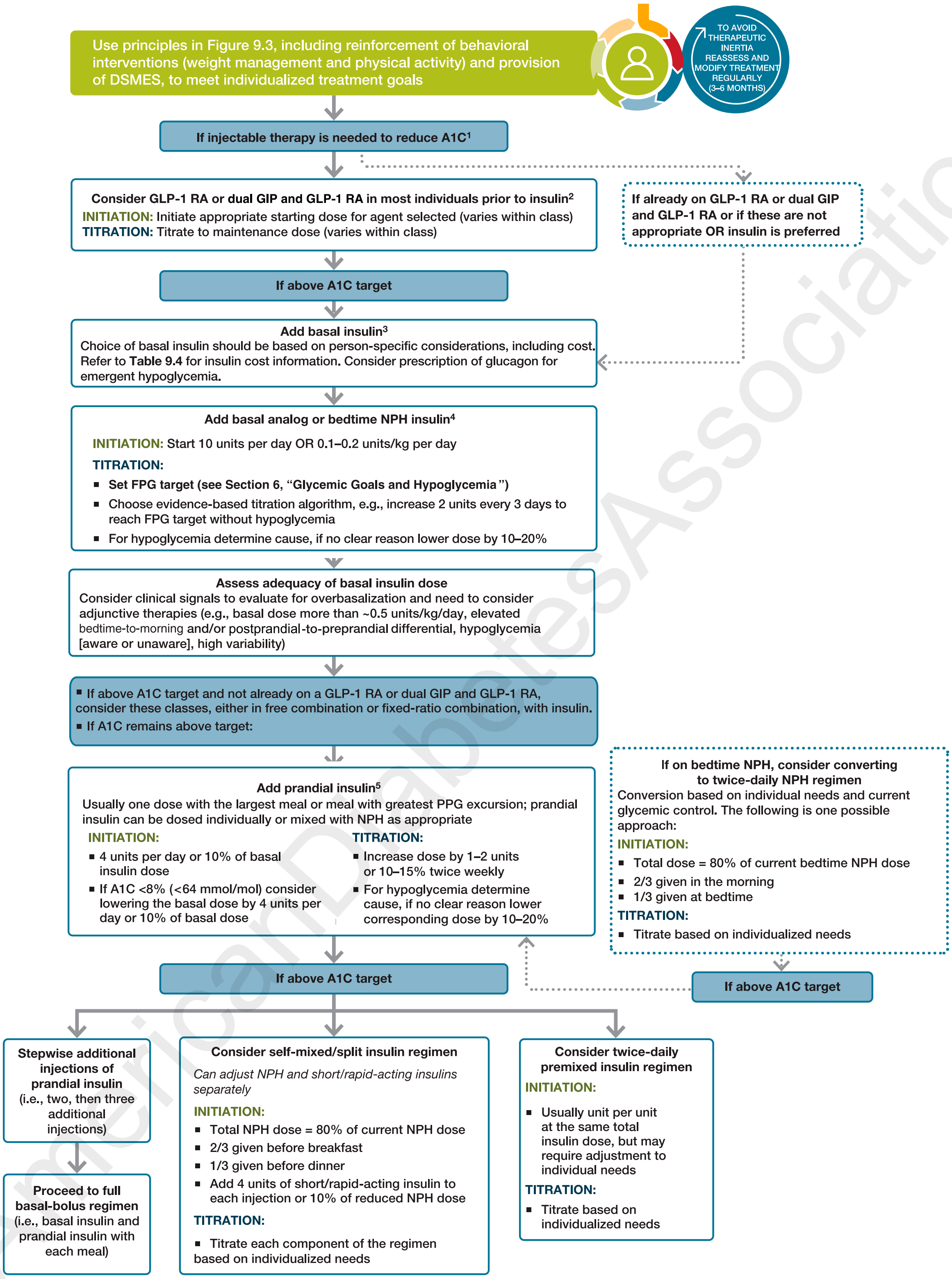
The cost of insulin has been rising steadily over the past two decades, at a pace severalfold that of other medical expenditures. This expense contributes significant burden to people with diabetes, as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct costs contribute to decrease in medication-taking behavior (130). As of January 2023, the cost of individual insulins was capped for enrollees in Medicare Part D plans (131), and at least 20 states and the District of Columbia have also capped insulin costs for enrollees in state-sponsored plans and, in select states, for those without insurance. In 2023, the three major U.S. insulin manufacturers also announced plans to reduce insulin prices; some plans go into effect in January 2024, and another has already occurred. The summary of the cost of insulin products in **Table 9.4** provides a comparison but is not reflective of the Medicare or state-level caps or the recent manufacturer price reductions. However, the information in **Table 9.4** reflects how the approval of unbranded versions (insulin aspart, lispro, degludec, glargine U-100, and some premixed products), follow-on products (insulin lispro and glargine), and interchangeable biosimilars (insulin glargine) have led to lower costs compared with other products. For some individuals with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance as well as those with cost concerns), human insulin (NPH and regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (132). Human regular insulin, NPH, and 70/30 NPH/regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.4** at select pharmacies. It is important to note that although these caps, price reductions, use of unbranded or biosimilar versions of analogs, or use of human insulins may impact the cost of insulin products, there are no caps on the costs of the other tools individuals with diabetes need for monitoring or treatment (including glucose monitoring supplies [strips or sensors], administration tools [pen needles, syringes, and insulin pumps], ketone testing supplies, and glucagon). Therefore, routine assessment of financial obstacles that may impact diabetes management is an important component of effective care of people with diabetes. Collaboration between members of the health care team and with social service professionals to identify and implement cost reduction strategies to support and improve access to evidence-based care is important (120,130).

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic goals. If an individual is not already being treated with a GLP-1 RA or dual GIP and GLP-1 RA, a GLP-1 RA (either as an individual product or in a fixed-ratio combination with a basal insulin product) or dual GIP and GLP-1 RA should be considered prior to prandial insulin to further address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy (84,114). For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin plan can then be intensified based on individual needs (**Fig. 9.4**). Individuals with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (∼1 unit/kg), and have lower rates of hypoglycemia (133). Titration can be based on home self-monitored blood glucose or CGM. When significant additions to the prandial insulin dose are made, particularly with the evening meal, consideration should be given to decreasing basal insulin. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported important differences in A1C or hypoglycemia (134,135).

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular


Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C1
Consider GLP-1 RA or dual GIP and GLP-1 RA in most individuals prior to insulin2
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or dual GIP and GLP-1 RA or if these are not appropriate OR insulin is preferred
If above A1C target
Add basal insulin3
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to Table 9.4 for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.
Add basal analog or bedtime NPH insulin4
INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day
TITRATION:
▪ Set FPG target (see Section 6, "Glycemic Goals and Hypoglycemia")
▪ Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
▪ For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime-to-morning and/or postprandial-to-preprandial differential, hypoglycemia [aware or unaware], high variability)
▪ If above A1C target and not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes, either in free combination or fixed-ratio combination, with insulin.
▪ If A1C remains above target:
Add prandial insulin5
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
▪ 4 units per day or 10% of basal insulin dose
▪ If A1C <8% (<64 mmol/mol) consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION:
▪ Increase dose by 1–2 units or 10–15% twice weekly
▪ For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%
If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
▪ Total dose = 80% of current bedtime NPH dose
▪ 2/3 given in the morning
▪ 1/3 given at bedtime
TITRATION:
▪ Titrate based on individualized needs
If above A1C target
If above A1C target
Stepwise additional injections of prandial insulin (i.e., two, then three additional injections)
Proceed to full basal-bolus regimen (i.e., basal insulin and prandial insulin with each meal)
Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
▪ Total NPH dose = 80% of current NPH dose
▪ 2/3 given before breakfast
▪ 1/3 given before dinner
▪ Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
▪ Titrate each component of the regimen based on individualized needs
Consider twice-daily premixed insulin regimen
INITIATION:
▪ Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
▪ Titrate based on individualized needs

1. Consider insulin as the first injectable if evidence of ongoing catabolism is present, symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVO is present. consider GLP-1 RA with proven CVO benefit. Oral or injectable GLP-1 RAs are appropriate.
3. For people on GLP-1 RA and basal Insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an A.M. dose of a long-acting basal Insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; dual GIP and GLP-1 RA, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (151).

Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/ product (if applicable)	Median AWP (min, max)*	Median NADAC (min, max)*	Maximum approved daily dose†
Biguanides	• Metformin	500 mg (ER)	$89 ($45, $6,719)	$5	2,000 mg
		850 mg (IR)	$108 ($5, $189)	$2	2,550 mg
		1,000 mg (IR)	$87 ($3, $144)	$2	2,000 mg
		1,000 mg (ER)	$1,884 ($242, $7,214)	$31 ($31, $226)	2,000 mg
		500 mg (Sol)	$405 ($405, $739)	$535	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$73 ($72, $198)	$3	8 mg
	• Glipizide	10 mg (IR)	$72 ($67, $91)	$6	40 mg
		10 mg (XL/ER)	$48 ($46, $48)	$10	20 mg
	• Glyburide	6 mg (micronized)	$54 ($48, $71)	$12	12 mg
		5 mg	$82 ($63, $432)	$8	20 mg
Thiazolidinedione	• Pioglitazone	45 mg	$348 ($7, $349)	$4	45 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $378)	$27	300 mg
	• Miglitol	100 mg	$294 ($241, $346)	NA	300 mg
Meglitinides	• Nateglinide	120 mg	$155	$27	360 mg
	• Repaglinide	2 mg	$878 ($58, $897)	$31	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$161	25 mg
	• Linagliptin	5 mg	$630	$504	5 mg
	• Saxagliptin	5 mg	$524	$466	5 mg
	• Sitagliptin	100 mg	$657	$525	100 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$718	$574	300 mg
	• Dapagliflozin	10 mg	$678	$543	10 mg
	• Empagliflozin	25 mg	$712	$569	25 mg
	• Ertugliflozin	15 mg	$408	$328	15 mg
GLP-1 RAs	• Dulaglutide	4.5 mg pen	$1,117	$895	4.5 mg‡
	• Exenatide	10 μg pen	$964	$771	20 μg
	• Exenatide (extended release)	2 mg pen	$990	$793	2 mg‡
	• Liraglutide	1.8 mg pen	$1,340	$1,072	1.8 mg
	• Semaglutide	1 mg pen	$1,123	$903	2 mg‡
		14 mg (tablet)	$1,097 ($1,070, $1,123)	$899	14 mg
Dual GIP and GLP-1 receptor agonist	• Tirzepatide	15 mg pen	$1,228	$982	15 mg‡
Bile acid sequestrant	• Colesevelam	625 mg tabs	$711 ($674, $712)	$64	3.75 g
		3.75 g suspension	$674 ($673, $675)	$130	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$1,200	$965	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,866	NA	120 μg/injection§

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. AWP and NADAC prices as of July 2023. *Calculated for 30-day supply (AWP [116] or NADAC [117] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. †Used to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. Prices for bexagliflozin were not available at the time of this update. ‡Administered once weekly. §AWP and NADAC calculated based on 120 μg three times daily.

insulin. U-500 regular insulin has distinct pharmacokinetics with similar onset but a delayed, blunted, and prolonged peak effect and longer duration of action compared with U-100 regular insulin; thus, it has characteristics more like a premixed intermediate-acting (NPH) and regular insulin product and can be used as two or three daily injections (136,137). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations, respectively, and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine but modestly lower efficacy per unit administered (138–140). The U-200 formulations of insulin degludec, insulin lispro, and insulin lispro-aabc have similar pharmacokinetics to their U-100 counterparts (141–143). These concentrated preparations may be more convenient (fewer injections to achieve target dose) and comfortable (less volume to inject target dose and/or less injection effort) for individuals and may improve treatment plan engagement in those with insulin resistance who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors. If U-500

Table 9.4—Median cost of insulin products in the U.S. calculated as AWP and NADAC per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Aspart	U-100 vial	$174†	$139†
		U-100 cartridge	$215†	$172†
		U-100 prefilled pen	$224†	$179†
	• Aspart ("faster acting product")	U-100 vial	$347	$277
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Glulisine	U-100 vial	$341	$273
		U-100 prefilled pen	$439	$351
	• Inhaled insulin	Inhalation cartridges	$1,503	NA
	• Lispro	U-100 vial	$30†	$24†
		U-100 cartridge	$408	$326
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$261
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	$338
	• Lispro follow-on product	U-100 vial	$118	$94
		U-100 prefilled pen	$151	$121
Short-acting	• Human regular	U-100 vial	$172 ($165, $178)‡	$137 ($132, $142)‡
		U-100 prefilled pen	$208	$166
Intermediate-acting	• Human NPH	U-100 vial	$172 ($165, $178)‡	$137 ($132, $143)‡
		U-100 prefilled pen	$208 ($208, $377)	$234 ($166, $303)
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Detemir	U-100 vial; U-100 prefilled pen	$370	$295
	• Degludec	U-100 vial	$142†	$327
		U-100 prefilled pen	$142†	$114†
		U-200 prefilled pen	$85†	$113†
	• Glargine	U-100 vial; U-100 prefilled pen	$136†	$109†
		U-300 prefilled pen	$363	$290
	• Glargine biosimilar/ follow-on products	U-100 prefilled pen	$190 ($74, $323)	$95†
		U-100 vial	$118†	$95†
Premixed insulin products	• Aspart 70/30	U-100 vial	$180†	$145†
		U-100 prefilled pen	$224†	$179†
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$341
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$127†	$102†
	• NPH/regular 70/30	U-100 vial	$172 ($165, $178)‡	$138 ($132, $143)‡
		U-100 prefilled pen	$208 ($208, $377)	$234 ($166, $302)
Premixed insulin/GLP-1 RA products	• Degludec/liraglutide	100/3.6 µg prefilled pen	$991	$795
	• Glargine/lixisenatide	100/33 µg prefilled pen	$679	$543

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP (116) and NADAC (117) prices as of July 2023. *AWP or NADAC calculated as in **Table 9.3**. †Unbranded product prices used when available. ‡AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

regular insulin vials are prescribed, the prescription should be accompanied by a prescription for U-500 syringes to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulin is primarily administered via subcutaneous injection or infusion. Administration devices provide some additional variation in the subcutaneous delivery beyond vial versus insulin pen. Those devices include continuous insulin pumps (programmable basal and bolus settings and fixed basal and bolus settings) and bolus-only insulin patch pump. In addition, prandial or correction insulin doses may be administered using inhaled human insulin. Inhaled insulin is available as monomers of regular human insulin; studies in individuals with type 1 diabetes suggest that inhaled insulin has pharmacokinetics similar to RAA (7). Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with the RAA insulin lispro, as well as clinically meaningful A1C reductions and weight reductions compared with the RAA insulin aspart over 24 weeks (144–146). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 second [FEV_1]). Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in individuals who smoke or who recently stopped smoking. All individuals require spirometry (FEV_1) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is $>$0.5 units/kg/day with indications of need for other therapy) and A1C remains above goal, consider advancing to combination injectable therapy (**Fig. 9.4**). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of insulin (114,147). The combination of basal insulin and GLP-1 RA (administered via separate injections of individual products or single injection of a fixed-ratio product) has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin plans (148). Two different once-daily, fixed dual combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide (iGlarLixi) and insulin degludec plus liraglutide (IDegLira). In select individuals with type 2 diabetes, complex insulin plans can also be simplified with fixed-ratio GLP-1 RA-insulin product (149).

Intensification of insulin treatment can be done by adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a plan with multiple prandial doses if necessary (150). Alternatively, for an individual on basal insulin in whom additional prandial coverage is desired but administering insulin prior to one or more meal(s) is not feasible, the medication plan can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal-prandial plans offer greater flexibility for individuals who eat on irregular schedules. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (70/30) formulations, are less costly alternatives to insulin analogs. **Figure 9.4** outlines these options as well as recommendations for further intensification, if needed, to achieve glycemic goals. When initiating intensification of insulin therapy, metformin, SGLT2 inhibitors, and GLP-1 RA (or dual GIP and GLP-1 RA) should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued. In individuals with suboptimal blood glucose management, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, although potential side effects should be considered. Once a basal-bolus insulin plan is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (also known as pattern control or pattern management). In some people with type 2 diabetes with significant clinical complexity, multimorbidity, and/or treatment burden, it may become necessary to simplify or deintensify complex insulin plans to decrease risk of hypoglycemia and improve quality of life (see Section 13, "Older Adults").

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10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S179–S218 | https://doi.org/10.2337/dc24-S010

*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

*For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "*Children and Adolescents.*"*

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral artery disease (PAD) presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and results in an estimated $39.4 billion in cardiovascular-related spending per year associated with diabetes (1). Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors (glycemic, blood pressure, and lipid control) are addressed simultaneously, with evidence for legacy benefits (2–4). Under the current paradigm of aggressive risk factor modification in people with diabetes, there is evidence that measures of 10-year CHD risk among U.S. adults with diabetes have improved significantly over the past decade (5) and that ASCVD morbidity and mortality have decreased (3,6).

Heart failure is another major cause of morbidity and mortality from cardiovascular disease. The American Diabetes Association (ADA) has developed a consensus report to summarize guidance for the screening, diagnosis, and treatment of people with diabetes (7). Recent studies have found that rates of incident heart failure hospitalization (adjusted for age and sex) were twofold higher in people with diabetes compared with those without (8,9). People with diabetes may present with a wide spectrum of heart failure, including heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmEF), or heart failure with reduced ejection fraction (HFrEF). Hypertension is often a precursor of heart failure of either type, and ASCVD can coexist with either type of heart failure (10), whereas prior myocardial infarction (MI) is often a major factor in HFrEF. Recent trials including people with type 2 diabetes, most of whom also had ASCVD, have shown

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**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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that rates of heart failure hospitalization significantly decreased with use of sodium–glucose cotransporter 2 (SGLT2) inhibitors (11–14).

A recent meta-analysis indicated that SGLT2 inhibitors reduce the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality in people with (secondary prevention) and without (primary prevention) cardiovascular disease (15).

For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all people with diabetes. These risk factors include duration of diabetes, obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence of albuminuria. Modifiable abnormal risk factors should be treated as described in these guidelines. Notably, the majority of evidence supporting interventions to reduce cardiovascular risk in diabetes comes from trials of people with type 2 diabetes. No randomized trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in people with type 1 diabetes. Therefore, the recommendations for cardiovascular risk factor modification for people with type 1 diabetes are extrapolated from data obtained in people with type 2 diabetes and are similar to those for people with type 2 diabetes.

As depicted in **Fig. 10.1**, a comprehensive approach to the reduction in risk of diabetes-related complications is recommended. Therapy that includes multiple, concurrent evidence-based approaches to care will provide complementary reduction in the risks of microvascular outcomes, including kidney, retinopathy, neurologic, and cardiovascular complications. Management of glycemia, blood pressure, and lipids and the incorporation of specific therapies with cardiovascular and kidney outcomes benefit (as individually appropriate) are considered fundamental elements of global risk reduction in diabetes.

THE RISK CALCULATOR

The American College of Cardiology ASCVD risk calculator (Risk Estimator Plus) is generally a useful tool to estimate 10-year risk of a first ASCVD event (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus). The calculator was developed to stratify cardiovascular risk and identify those people who will benefit most from statin therapy and from treatment with antihypertensive medications (16). The calculator includes diabetes as a risk factor, since diabetes itself confers increased risk for ASCVD, although it should be acknowledged that these risk calculators do not account for the duration of diabetes or the presence of diabetes complications, such as albuminuria. In addition, the majority of people with diabetes should be treated with statin therapy, and hypertension should be promptly treated. As we will discuss below, comprehensive management of hypertension, hyperlipidemia, and hyperglycemia using management approaches with established benefit are important strategies to reduce cardiovascular risk.

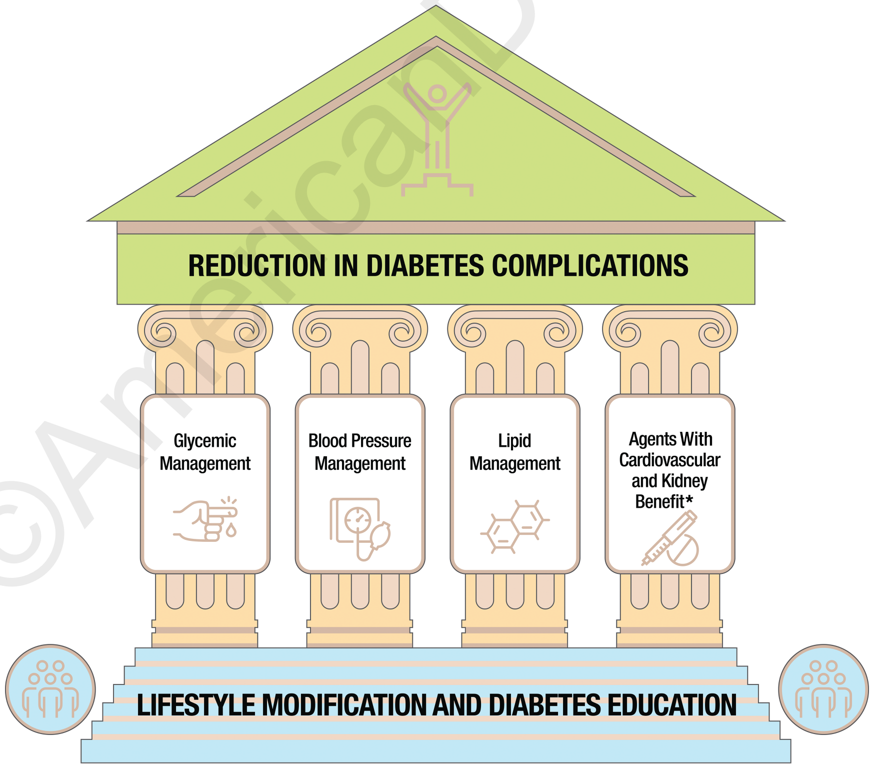
REDUCTION IN DIABETES COMPLICATIONS
Glycemic Management
Blood Pressure Management
Lipid Management
Agents With Cardiovascular and Kidney Benefit*
LIFESTYLE MODIFICATION AND DIABETES EDUCATION

Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

HYPERTENSION/BLOOD PRESSURE CONTROL

An elevated blood pressure is defined as a systolic blood pressure 120–129 mmHg and a diastolic blood pressure $<$80 mmHg (17). Hypertension is defined as a systolic blood pressure $\geq$130 mmHg or a diastolic blood pressure $\geq$80 mmHg (17). This is in agreement with the definition of hypertension by the American College of Cardiology and American Heart Association (17). Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for ASCVD, heart failure, and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the ADA position statement "Diabetes and Hypertension" for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (18) and recent updated hypertension guideline recommendations (17,19,20).

Screening and Diagnosis

Recommendations

10.1 Blood pressure should be measured at every routine clinical visit. When possible, individuals found to have elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic $<$80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure $\geq$130 mmHg or a diastolic blood pressure $\geq$80 mmHg based on an average of two or more measurements obtained on two or more occasions. **A** Individuals with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**

10.2 All people with hypertension and diabetes should be counseled to monitor their blood pressure at home after appropriate education. **A**

Blood pressure should be measured at every routine clinical visit by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference (21). Elevated values should preferably be confirmed on a separate day; however, in individuals with cardiovascular disease and blood pressure ≥180/110 mmHg, it is reasonable to diagnose hypertension at a single visit (19). Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and "true" blood pressure (22,23). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. Studies of individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (22,23). Moreover, home blood pressure monitoring may improve medication-taking behavior and thus help reduce cardiovascular risk (24).

Treatment Goals

Recommendations

10.3 For people with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and individual preferences. **B**

10.4 The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. **A**

10.5 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational-age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be deintensified for blood pressure <90/60 mmHg. **E** A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

Randomized clinical trials have demonstrated unequivocally that treatment of hypertension reduces cardiovascular events as well as microvascular complications (25–31). There has been controversy on the recommendation of a specific blood pressure goal in people with diabetes. The committee recognizes that there has been no randomized controlled trial to specifically demonstrate a decreased incidence of cardiovascular events in people with diabetes by targeting a blood pressure <130/80 mmHg. The recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association (18), the International Society of Hypertension (19), and the European Society of Cardiology (20). The committee's recommendation for the blood pressure target of <130/80 mmHg derives primarily from the collective evidence of the following randomized controlled trials. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treatment to a target systolic blood pressure of <120 mmHg decreases cardiovascular event rates by 25% in high-risk individuals, although people with diabetes were excluded from this trial (32). The recently completed Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial included nearly 20% of people with diabetes and noted decreased cardiovascular events with treatment of hypertension to a blood pressure target of <130 mmHg (33). While the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial (ACCORD BP) did not confirm that targeting a systolic blood pressure of <120 mmHg in people with diabetes results in decreased cardiovascular event rates, the prespecified secondary outcome of stroke was reduced by 41% with intensive treatment (34). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial revealed that treatment with perindopril/indapamide to an achieved systolic blood pressure of ∼135 mmHg significantly decreased cardiovascular event rates compared with a placebo treatment with an achieved blood pressure of 140 mmHg (35). Therefore, it is recommended that people with diabetes who have hypertension should be treated to blood pressure targets of <130/80 mmHg. Notably, there is an absence of high-quality data available to guide blood pressure targets in people with type 1 diabetes, but a similar blood pressure target of <130/80 mmHg is recommended in people with type 1 diabetes. As discussed below, treatment should be individualized, and treatment should not be targeted to <120/80 mmHg, as a mean achieved blood pressure of <120/80 mmHg is associated with adverse events.

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

SPRINT provides the strongest evidence to support lower blood pressure goals in individuals at increased cardiovascular risk, although this trial excluded people with diabetes (32). The trial enrolled 9,361 individuals with a systolic blood pressure of ≥130 mmHg and increased cardiovascular risk and treated to a systolic blood pressure target of <120 mmHg (intensive treatment) versus a target of <140 mmHg (standard treatment). The primary composite outcome of MI, coronary syndromes, stroke, heart failure, or death from cardiovascular causes was reduced by 25% in the intensive treatment group. The achieved systolic blood pressures in the trial were 121 mmHg and 136 mmHg in the intensive versus standard treatment group, respectively. Adverse outcomes, including hypotension, syncope, electrolyte abnormality, and acute kidney injury (AKI), were more common in the intensive treatment arm; risk of adverse outcomes needs to be weighed against the cardiovascular benefit of more intensive blood pressure lowering.

ACCORD BP provides the strongest direct assessment of the benefits and risks of intensive blood pressure control in people with type 2 diabetes (34). In the study, a total of 4,733 individuals with type 2 diabetes were assigned to intensive therapy (targeting a systolic blood pressure <120 mmHg) or standard therapy (targeting a systolic blood pressure <140 mmHg). The mean achieved systolic blood pressures were 119 mmHg and 133 mmHg in the intensive versus standard group, respectively. The primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes was not significantly reduced in the intensive treatment group. The prespecified secondary outcome of stroke was significantly reduced by 41% in the intensive treatment group. Adverse events attributed to blood pressure treatment, including hypotension, syncope, bradycardia, hyperkalemia, and elevations in serum creatinine, occurred more frequently in the intensive treatment arm than in the standard therapy arm (**Table 10.1**).

Of note, the ACCORD BP and SPRINT trials targeted a similar systolic blood pressure <120 mmHg, but in contrast to SPRINT, the primary composite cardiovascular end point was nonsignificantly reduced in ACCORD BP. The results have been interpreted to be generally consistent between both trials, but ACCORD BP was viewed as underpowered due to the composite primary end point being less sensitive to blood pressure regulation (32).

The more recent STEP trial assigned 8,511 individuals aged 60–80 years with hypertension to a systolic blood pressure target of 110 to <130 mmHg (intensive treatment) or a target of 130 to <150 mmHg (33). In this trial, the primary composite outcome of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes occurred in 3.5% of individuals in the intensive treatment group versus 4.6% in the standard treatment group (hazard ratio [HR] 0.74 [95% CI 0.60–0.92]; *P* = 0.007). In this trial, 18.9% of individuals in the intensive treatment arm and 19.4% in the standard treatment arm had a diagnosis of type 2 diabetes. Hypotension occurred more frequently in the intensive treatment group (3.4%) compared with the standard treatment group (2.6%), without significant differences in other adverse events, including dizziness, syncope, or fractures.

In ADVANCE, 11,140 people with type 2 diabetes were randomized to receive either treatment with a fixed combination of perindopril/indapamide or matching placebo (35). The primary end point, a composite of cardiovascular death, nonfatal stroke infarction, or worsening renal or diabetic eye disease, was reduced by 9% in the combination treatment. The achieved systolic blood pressure was ∼135 mmHg in the treatment group and 140 mmHg in the placebo group.

The Hypertension Optimal Treatment (HOT) trial enrolled 18,790 individuals and targeted diastolic blood pressure <90 mmHg, <85 mmHg, or <80 mmHg (36). The cardiovascular event rates, defined as fatal or nonfatal MI, fatal and nonfatal strokes, and all other cardiovascular events, were not significantly different between diastolic blood pressure targets (≤90 mmHg, ≤85 mmHg, and ≤80 mmHg), although the lowest incidence of cardiovascular events occurred with an achieved diastolic blood pressure of 82 mmHg. However, in people with diabetes, there was a significant 51% reduction in the treatment group with a target diastolic blood pressure of <80 mmHg compared with a target diastolic blood pressure of <90 mmHg.

Meta-analyses of Trials

To clarify optimal blood pressure targets in people with diabetes, multiple meta-analyses have been performed. One of the largest meta-analyses included 73,913 people with diabetes. Compared with a less tight blood pressure control, allocation to a tighter blood pressure control significantly reduced the risk of stroke by 31% but did not reduce the risk of MI (37). Another meta-analysis of 19 trials that included 44,989 individuals showed that a mean blood pressure of 133/76 mmHg is associated with a 14% risk reduction for major cardiovascular events compared with a mean blood pressure of 140/81 mmHg (31). This benefit was greatest in people with diabetes. An analysis of trials including people with type 2 diabetes and impaired glucose tolerance with achieved systolic blood pressures of <135 mmHg in the intensive blood pressure treatment group and <140 mmHg in the standard treatment group revealed a 10% reduction in all-cause mortality and a 17% reduction in stroke (29). More intensive reduction to <130 mmHg was associated with a further reduction in stroke but not other cardiovascular events.

Several meta-analyses stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be most beneficial when mean baseline blood pressure is ≥140/90 mmHg (17,25,26,28–30). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident.

Individualization of Treatment Targets

People with diabetes and clinicians should engage in a shared decision-making process to determine individual blood pressure targets (17). This approach acknowledges that the benefits and risks of intensive blood pressure targets are uncertain and may vary across individuals and is consistent with a person-focused approach to care that values individual priorities and health care professional judgment (38). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help determine individuals more likely to benefit and less likely to be harmed by intensive blood pressure control (39,40).

Absolute benefit from blood pressure reduction correlated with absolute baseline cardiovascular risk in SPRINT and in earlier clinical trials conducted at higher baseline blood pressure levels (40,41). Extrapolation of these studies suggests that people with diabetes may also be more likely to benefit from intensive blood pressure control when they have high absolute cardiovascular risk. This approach is consistent with guidelines from the American College of Cardiology and American Heart Association, which also advocate a blood pressure target of <130/80 mmHg for all people, with or without diabetes (18).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, AKI, and electrolyte abnormalities) should also be taken into account (32,34,42,43). Individuals with older age, CKD, and frailty have been shown to be at higher risk of adverse effects of intensive blood pressure control (42). In addition, individuals with orthostatic hypotension, substantial comorbidity, functional limitations,

Table 10.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (34)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE (35)	11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (310)
HOT (36)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (42)	9,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI
STEP (33)	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) • Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes.

or polypharmacy may be at high risk of adverse effects, and some individuals may prefer higher blood pressure targets to enhance quality of life. However, ACCORD BP demonstrated that intensive blood pressure lowering decreased the risk of cardiovascular events irrespective of baseline diastolic blood pressure in individuals who also received standard glycemic control (44). Therefore, the presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care.

Pregnancy and Antihypertensive Medications

There are few randomized controlled trials of antihypertensive therapy in pregnant individuals with diabetes. A 2018 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension included 63 trials and over 5,909 women and suggested that antihypertensive therapy probably reduces the risk of developing severe hypertension but may not affect the risk of fetal or neonatal death, small-for-gestational-age babies, or preterm birth (45). The Control of Hypertension in Pregnancy Study (CHIPS) (46) enrolled mostly women with chronic hypertension. In CHIPS, targeting a diastolic blood pressure of 85 mmHg during pregnancy was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for infants compared with targeting a higher diastolic blood pressure. The mean systolic blood pressure achieved in the more intensively treated group was 133.1 ± 0.5 mmHg, and the mean diastolic blood pressure achieved in that group was 85.3 ± 0.3 mmHg. A similar approach is supported by the International Society for the Study of Hypertension in Pregnancy, which specifically recommends use of antihypertensive therapy to maintain systolic blood pressure between 110 and 140 mmHg and diastolic blood pressure between 80 and 85 mmHg (47).

The more recent Chronic Hypertension and Pregnancy (CHAP) trial assigned pregnant individuals with mild chronic hypertension to antihypertensive medications to target a blood pressure goal of $<$140/90 mmHg (active treatment group) or to control treatment, in which antihypertensive therapy was withheld unless severe hypertension (systolic pressure $\geq$160 mmHg or diastolic pressure $\geq$105 mmHg) developed (control group) (48). The primary outcome, a composite of preeclampsia with severe features, medically indicated preterm birth at $<$35 weeks of gestation, placental abruption, or fetal/neonatal death, occurred in 30.2% of female participants in the active treatment group versus 37.0% in the control group ($P < 0.001$). The mean systolic blood pressure between randomization and delivery was 129.5 mmHg in the active treatment group and 132.6 mmHg in the control group.

Current evidence supports controlling blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension but also to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors, and spironolactone are contraindicated, as they may cause fetal damage. Special consideration should be taken for individuals of childbearing potential, and people intending to become pregnant should switch from an ACE inhibitor/ARB or spironolactone to an alternative antihypertensive medication approved during pregnancy. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralazine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (49). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (49,50). The American College of Obstetricians and Gynecologists also recommends that postpartum individuals with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and 7–10 days postpartum. Long-term follow-up is recommended for these individuals, as they have increased lifetime cardiovascular risk (51). See Section 15, “Management of Diabetes in Pregnancy,” for additional information.

Treatment Strategies

Lifestyle Intervention

Recommendation

10.6 For people with blood pressure $>$120/80 mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)–style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, smoking cessation, and increased physical activity. **A**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”), at least 150 min of moderate-intensity aerobic activity per week (see Section 3, “Prevention or Delay of Diabetes and Associated Comorbidities”), restricting sodium intake ($<$2,300 mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (52), and increasing activity levels (53) (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”).

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic $>$120 mmHg or diastolic $>$80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (**Fig. 10.2**) (53). A lifestyle therapy plan should be developed in collaboration with the person with diabetes and discussed as part of diabetes management. Use of internet or mobile-based digital platforms to reinforce healthy behaviors may be considered as a component of care, as these interventions have been found to enhance the efficacy of medical therapy for hypertension (54,55).

Pharmacologic Interventions

Recommendations

10.7 Individuals with confirmed office-based blood pressure $\geq$130/80 mmHg qualify for initiation and titration of pharmacologic therapy to achieve the recommended blood pressure goal of $<$130/80 mmHg. **A**

10.8 Individuals with confirmed office-based blood pressure $\geq$150/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes. **A**

10.9 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. **A** ACE inhibitors or angiotensin receptor blockers (ARBs) are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A**

10.10 Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs (including ARBs/neprilysin inhibitors) with direct renin inhibitors should not be used. **A**

10.11 An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio $\geq$300 mg/g

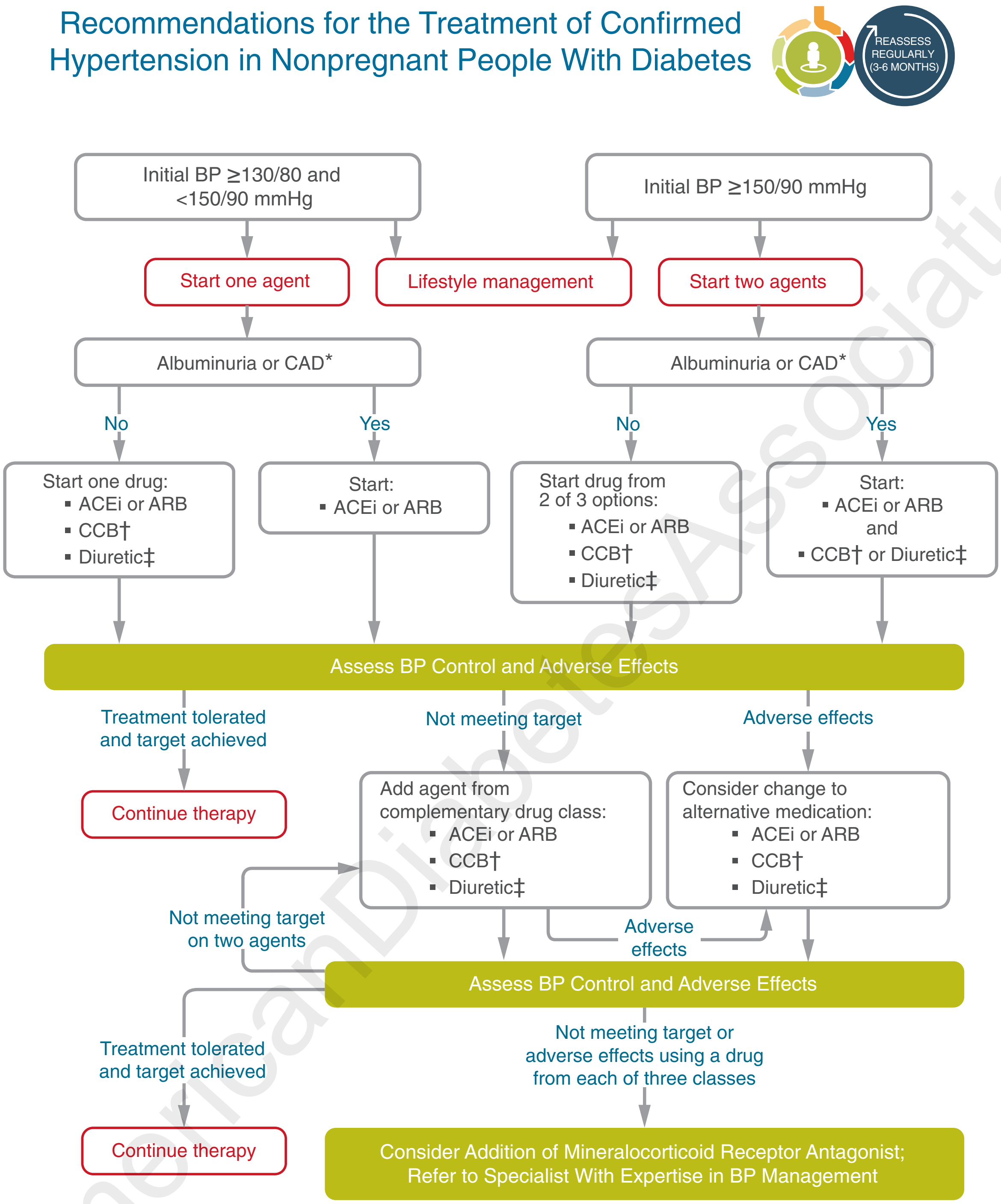
Recommendations for the Treatment of Confirmed Hypertension in Nonpregnant People With Diabetes
REASSESS REGULARLY (3-6 MONTHS)
Initial BP ≥130/80 and <150/90 mmHg
Initial BP ≥150/90 mmHg
Start one agent
Lifestyle management
Start two agents
Albuminuria or CAD*
Albuminuria or CAD*
No
Yes
No
Yes
Start one drug:
▪ ACEi or ARB
▪ CCB†
▪ Diuretic‡
Start:
▪ ACEi or ARB
Start drug from 2 of 3 options:
▪ ACEi or ARB
▪ CCB†
▪ Diuretic‡
Start:
▪ ACEi or ARB
and
▪ CCB† or Diuretic‡
Assess BP Control and Adverse Effects
Treatment tolerated and target achieved
Not meeting target
Adverse effects
Continue therapy
Add agent from complementary drug class:
▪ ACEi or ARB
▪ CCB†
▪ Diuretic‡
Consider change to alternative medication:
▪ ACEi or ARB
▪ CCB†
▪ Diuretic‡
Not meeting target on two agents
Adverse effects
Assess BP Control and Adverse Effects
Treatment tolerated and target achieved
Not meeting target or adverse effects using a drug from each of three classes
Continue therapy
Consider Addition of Mineralocorticoid Receptor Antagonist; Refer to Specialist With Expertise in BP Management

Figure 10.2—Recommendations for the treatment of confirmed hypertension in nonpregnant people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. †Dihydropyridine calcium channel blocker (CCB). ‡Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. BP, blood pressure. Adapted from de Boer et al. (18).

creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**

10.12 For adults treated with an ACE inhibitor, ARB, mineralocorticoid receptor antagonist (MRA), or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored within 7–14 days after initiation of therapy and at least annually. **B**

Initial Number of Antihypertensive Medications. Initial treatment for people with diabetes depends on the severity of hypertension (**Fig. 10.2**). Those with blood pressure between 130/80 mmHg and 150/90 mmHg may begin with a single drug. For individuals with blood pressure ≥150/90 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended in order to more effectively achieve adequate blood pressure control (56–58). Single-pill antihypertensive combinations may improve medication taking in some individuals (59).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes: ACE inhibitors (60,61), ARBs (60,61), thiazide-like diuretics (62), or dihydropyridine calcium channel blockers (63). In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (64–66). For individuals with albuminuria (urine albumin-to-creatinine ratio [UACR] $\geq$30 mg/g), initial treatment should include an ACE inhibitor or ARB to reduce the risk of progressive kidney disease (18) (**Fig. 10.2**). In individuals receiving ACE inhibitor or ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease (67). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (68). β-Blockers are indicated in the setting of prior MI, active angina, or HFrEF but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions (27,69,70).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure targets (**Fig. 10.2**), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is contraindicated given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and AKI (71–73). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure targets.

Bedtime Dosing. Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications (74,75), these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended (76).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors/ARBs or mineralocorticoid receptor antagonists (MRAs) can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (77,78). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (79). Therefore, serum creatinine and potassium should be monitored after initiation of treatment with an ACE inhibitor/ARB, MRA, or diuretic and monitored during treatment and following uptitration of these medications, particularly among individuals with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (77,78,80).

Resistant Hypertension

Recommendation

10.13 Individuals with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for MRA therapy. **A**

Resistant hypertension is defined as blood pressure $\geq$140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs with complementary mechanisms of action at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including missed doses of antihypertensive medications, white coat hypertension, and secondary hypertension. People with diabetes and confirmed resistant hypertension should be evaluated for secondary causes of hypertension, including primary hyperaldosteroism, renal artery stenosis, diabetic kidney disease, and obstructive sleep apnea. In general, barriers to medication taking (such as cost and side effects) should be identified and addressed (**Fig. 10.2**). MRAs, including spironolactone and eplerenone, are effective for management of resistant hypertension in people with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker (81). In addition, MRAs reduce albuminuria in people with diabetic nephropathy (82–84). However, adding an MRA to a treatment plan that includes an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these individuals, and long-term outcome studies are needed to better evaluate the role of MRAs in blood pressure management.

LIPID MANAGEMENT

Lifestyle Intervention

Recommendations

10.14 Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or DASH eating pattern; reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanol/sterol intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD) in people with diabetes. **A**

10.15 Intensify lifestyle therapy and optimize glycemic control for people with diabetes with elevated triglyceride levels ($\geq$150 mg/dL [$\geq$1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women). **C**

Lifestyle intervention, including weight loss in people with overweight or obesity (when appropriate) (85), increased physical activity, and medical nutrition therapy, allows some individuals to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each person's age, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean (83) or Dietary Approaches to Stop Hypertension (DASH) eating pattern, reducing saturated and *trans* fat intake, and increasing plant stanol/sterol, n-3 fatty acid, and viscous fiber (such as in oats, legumes, and citrus) intake (86,87). Glycemic control may also beneficially modify plasma lipid levels, particularly in people with very high triglycerides and poor glycemic control. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional nutrition information.

Ongoing Therapy and Monitoring With Lipid Panel

Recommendations

10.16 In adults with prediabetes or diabetes not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diagnosis, at an initial medical evaluation, annually thereafter, or more frequently if indicated. **E**

10.17 Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter, as it may help to monitor the response to therapy and inform medication taking. **A**

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in individuals $<$40 years of age. In younger people with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once an individual is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and annually (e.g., to monitor for medication taking and efficacy). Monitoring lipid profiles after initiation of statin therapy and during therapy increases dose titration and statin adherence (88–90). If LDL cholesterol levels are not responding in spite of medication taking, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood (91). Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less than daily statin doses (92).

STATIN TREATMENT

Primary Prevention

Recommendations

10.18 For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**

10.19 For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**

10.20 For people with diabetes aged 40–75 years at higher cardiovascular risk, including those with one or more ASCVD risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by $\geq$50% of baseline and to target an LDL cholesterol goal of $<$70 mg/dL ($<$1.8 mmol/L). **A**

10.21 For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple ASCVD risk factors and an LDL cholesterol $\geq$70 mg/dL ($\geq$1.8 mmol/L), it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **B**

10.22 In adults with diabetes aged $>$75 years already on statin therapy, it is reasonable to continue statin treatment. **B**

10.23 In adults with diabetes aged $>$75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks. **C**

10.24 In people with diabetes intolerant to statin therapy, treatment with bempedoic acid is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan. **A**

10.25 Statin therapy is contraindicated in pregnancy. **B**

Secondary Prevention

Recommendations

10.26 For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.27 For people with diabetes and ASCVD, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of $\geq$50% from baseline and an LDL cholesterol goal of $<$55 mg/dL ($<$1.4 mmol/L). Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**

10.28a For individuals who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used. **E**

10.28b For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **A** bempedoic acid therapy, **A** or PCSK9 inhibitor therapy with inclisiran siRNA **E** should be considered as an alternative cholesterol-lowering therapy.

Initiating Statin Therapy Based on Risk

People with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without CHD (93,94). Subgroup analyses of people with diabetes in larger trials (95–99) and trials in people with diabetes (100,101) showed significant primary and secondary prevention of ASCVD events and CHD death in people with diabetes. Meta-analyses including data from over 18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years) demonstrated a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (102). The cardiovascular benefit in this large meta-analysis did not depend on baseline LDL cholesterol levels and was linearly related to the LDL cholesterol reduction without a low threshold beyond which there was no benefit observed (102).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 10.2** shows the two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve an approximately $\geq$50% reduction in LDL cholesterol, and moderate-intensity statin plans achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in people with diabetes but is sometimes the only dose of statin that an individual can tolerate. For individuals who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.

Table 10.2—High-intensity and moderate-intensity statin therapy

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

Once-daily dosing. XL, extended release.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing (103,104). The relative benefit of lipid-lowering therapy has been uniform across most subgroups tested (94,102), including subgroups that varied with respect to age and other risk factors.

Primary Prevention (People Without ASCVD)

For primary prevention, moderate-dose statin therapy is recommended for those aged ≥40 years (96,103,104), although high-intensity therapy should be considered in the context of additional ASCVD risk factors. The evidence is strong for people with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit. Since cardiovascular risk is enhanced in people with diabetes, as noted above, individuals who also have multiple other coronary risk factors have increased risk, equivalent to that of those with ASCVD. Therefore, current guidelines recommend that in people with diabetes who are at higher cardiovascular risk, especially those with one or more ASCVD risk factors, high-intensity statin therapy should be prescribed to reduce LDL cholesterol by ≥50% from baseline and to target an LDL cholesterol of <70 mg/dL (<1.8 mmol/L) (105–107). Since, in clinical practice, it is frequently difficult to ascertain the baseline LDL cholesterol level prior to statin therapy initiation, in those individuals, a focus on an LDL cholesterol target level of <70 mg/dL (<1.8 mmol/L) rather than the percent reduction in LDL cholesterol is recommended. In those individuals, it may also be reasonable to add ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy to maximum tolerated statin therapy if needed to reduce LDL cholesterol levels by ≥50% and to achieve the recommended LDL cholesterol target of <70 mg/dL (<1.8 mmol/L) (108). While there are no randomized controlled trials specifically assessing cardiovascular outcomes of adding ezetimibe or PCSK9 inhibitors to statin therapy in primary prevention, the Open-Label Study of Long-term Evaluation Against LDL Cholesterol (OSLER) study included ∼80% of study participants without established cardiovascular disease. In the treatment group, LDL cholesterol was reduced by 61%, and, although exploratory and not a primary outcome, cardiovascular events were reduced by 18% in the standard-therapy group to 0.95% in the evolocumab group (HR in the evolocumab group 0.47 [95% CI 0.28–0.78]; *P* = 0.003) (109). Similarly, the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy (ODYSSEY LONG TERM) included ∼30% of study participants without established cardiovascular disease and 33% of people with diabetes. Alirocumab added to statin therapy reduced LDL cholesterol by 62% and major adverse cardiovascular events in a post hoc analysis (1.7% vs. 3.3% compared with placebo; HR 0.52 [95% CI 0.31–0.90]; nominal *P* = 0.02) (110). In addition, a meta-analysis suggests that there is a cardiovascular benefit of adding ezetimibe or PCSK9 inhibitors to treatment for high-risk people (111). The evidence is lesser for individuals aged >75 years; relatively few older people with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (94,101,102), and because older age confers higher risk, the absolute benefits are actually greater (94,112). Moderate-intensity statin therapy is recommended in people with diabetes who are ≥75 years of age. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose performed as needed. See Section 13, "Older Adults," for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes. Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type 1 diabetes of any age. For pediatric recommendations, see Section 14, "Children and Adolescents." In the Heart Protection Study (lower age limit 40 years), the subgroup of ∼600 people with type 1 diabetes had a reduction in risk proportionately similar, although not statistically significant, to that in people with type 2 diabetes (96). Even though the data are not definitive, similar statin treatment approaches should be considered for people with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Individuals <40 years of age have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high. For people who are <40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the individual and health care professional discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to "Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association" (113) for additional discussion.

Secondary Prevention (People With ASCVD)

Because cardiovascular event rates are increased in people with diabetes and established ASCVD, intensive therapy is indicated and has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials (94,102,112,114,115). High-intensity statin therapy is recommended for all people with diabetes and ASCVD to target an

LDL cholesterol reduction of $\geq$50% from baseline and an LDL cholesterol goal of $<$55 mg/dL ($<$1.4 mmol/L). Based on the evidence discussed below, addition of ezetimibe or a PCSK9 inhibitor is recommended if this goal is not achieved on maximum tolerated statin therapy. These recommendations are based on the observation that high-intensity versus moderate-intensity statin therapy reduces cardiovascular event rates in high-risk individuals with established cardiovascular disease in randomized trials (98,114). In addition, the Cholesterol Treatment Trialists' Collaboration, involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins (102), showed a 21% reduction in major cardiovascular events in people with diabetes for every 39 mg/dL (1 mmol/L) of LDL cholesterol lowering, irrespective of baseline LDL cholesterol or individual characteristics (102). However, the best evidence to support lower LDL cholesterol targets in people with diabetes and established cardiovascular disease derives from multiple large randomized trials investigating the benefits of adding nonstatin agents to statin therapy. As discussed in detail below, these include combination treatment with statins and ezetimibe (112,116) or PCSK9 inhibitors (115,117–119). Each trial found a significant benefit in the reduction of ASCVD events that was directly related to the degree of further LDL cholesterol lowering. These large trials included a significant number of participants with diabetes and prespecified analyses on cardiovascular outcomes in people with and without diabetes (116,118,119). The decision to add a nonstatin agent should be made following a discussion between a clinician and a person with diabetes about the net benefit, safety, and cost of combination therapy.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial in 18,144 individuals comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone (112). Individuals were $\geq$50 years of age, had experienced a recent acute coronary syndrome, and were treated for an average of 6 years. Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events (atherosclerotic cardiovascular events), with the degree of benefit being directly proportional to the change in LDL cholesterol, which was 70 mg/dL (1.8 mmol/L) in the statin group on average and 54 mg/dL (1.4 mmol/L) in the combination group (112). In those with diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45% cumulative incidence at 7 years) and a relative risk reduction of 14% (HR 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (116).

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximum tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36 to 59%. These agents have been approved as adjunctive therapy for individuals with ASCVD or familial hypercholesterolemia who are receiving maximum tolerated statin therapy but require additional lowering of LDL cholesterol (120,121). No cardiovascular outcome trials have been performed to assess whether PCSK9 inhibitor therapy reduces ASCVD event rates in individuals without established cardiovascular disease (primary prevention).

The effects of PCSK9 inhibition on ASCVD outcomes were investigated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, which enrolled 27,564 individuals with prior ASCVD and an additional high-risk feature who were receiving their maximum tolerated statin therapy (two-thirds were on high-intensity statin) but who still had LDL cholesterol $\geq$70 mg/dL ($\geq$1.8 mmol/L) or non-HDL cholesterol $\geq$100 mg/dL ($\geq$2.6 mmol/L) (115). Individuals were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month based on individual preference) versus placebo. Evolocumab reduced LDL cholesterol by 59% from a median of 92 down to 30 mg/dL in the treatment arm.

During the median follow-up of 2.2 years, the composite outcome of cardiovascular death, MI, stroke, hospitalization for angina, or revascularization occurred in 11.3% vs. 9.8% of the placebo and evolocumab groups, respectively, representing a 15% relative risk reduction ($P < 0.001$). The combined end point of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4 to 5.9% ($P < 0.001$). Evolocumab therapy also significantly reduced all strokes (1.5% vs. 1.9%; HR 0.79 [95% CI 0.66–0.95]; $P = 0.01$) and ischemic stroke (1.2% vs. 1.6%; HR 0.75 [95% CI 0.62–0.92]; $P = 0.005$) in the total population, with findings being consistent in individuals with or without a history of ischemic stroke at baseline (122). Importantly, similar benefits were seen in a prespecified subgroup of people with diabetes, comprising 11,031 individuals (40% of the trial) (119).

In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 18,924 individuals (28.8% of whom had diabetes) with recent acute coronary syndrome were randomized to the PCSK9 inhibitor alirocumab or placebo every 2 weeks in addition to maximum tolerated statin therapy, with alirocumab dosing titrated between 75 and 150 mg to achieve LDL cholesterol levels between 25 and 50 mg/dL (117). Over a median follow-up of 2.8 years, a composite primary end point (comprising death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospital admission) occurred in 903 individuals (9.5%) in the alirocumab group and in 1,052 individuals (11.1%) in the placebo group (HR 0.85 [95% CI 0.78–0.93]; $P < 0.001$). Combination therapy with alirocumab plus statin therapy resulted in a greater absolute reduction in the incidence of the primary end point in people with diabetes (2.3% [95% CI 0.4–4.2]) than in those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [–0.3 to 2.7]) (118).

In addition to monoclonal antibodies targeting PCSK9, the siRNA inclisiran has been developed and has recently become available in the U.S. In the Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10) and

Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trials (123), individuals with established cardiovascular disease or ASCVD risk equivalent were randomized to receive inclisiran or placebo. Inclisiran allows less frequent administration compared with monoclonal antibodies and was administered on day 1, on day 90, and every 6 months in these trials. In the ORION-10 trial, 47.5% of individuals in the inclisiran group and 42.4% in the placebo group had diabetes; in the ORION-11 trial, 36.5% of individuals in the inclisiran group and 33.7% in the placebo group had diabetes. The coprimary end point of placebo-corrected percent change in LDL cholesterol level from baseline to day 510 was 52.3% in the ORION-10 trial and 49.9% in the ORION-11 trial. In an exploratory analysis, the prespecified cardiovascular end point, defined as a cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal MI, or stroke, occurred in 7.4% of the inclisiran group and 10.2% of the placebo group in the ORION-10 trial and in 7.8% of the inclisiran group and 10.3% of the placebo group in the ORION-11 trial. A cardiovascular outcome trial using inclisiran in people with established cardiovascular disease is currently ongoing (124).

Intolerance to Statin Therapy

Statin therapy is a hallmark approach to cardiovascular prevention and treatment; however, a subset of individuals experience partial (inability to tolerate sufficient dosage necessary to achieve therapeutic objectives due to adverse effects) or complete (inability to tolerate any dose) intolerance to statin therapy (125). Although the definition of statin intolerance differs between organizations and within clinical study methods, these individuals will require an alternative treatment approach. Initial steps in people intolerant to statins may include switching to a different high-intensity statin if a high-intensity statin is indicated, switching to moderate-intensity or low-intensity statin, lowering the statin dose, or using nondaily dosing of statins. While considering these alternative treatment plans, the addition of nonstatin treatment plans to maximum tolerated statin therapy should be considered, as these are frequently associated with improved adherence and target LDL cholesterol goal achievement (125).

PCSK9 Inhibition

The PCSK9 monoclonal antibodies alirocumab and evolocumab have both been studied within populations considered statin intolerant. The Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular Risk, Who Are Intolerant to Statins (ODYSSEY ALTERNATIVE) trial evaluated the LDL cholesterol–lowering efficacy of alirocumab compared with ezetimibe in addition to the safety of each of the prior two treatments compared with a statin rechallenge arm with 20 mg atorvastatin in 314 individuals with primary hypercholesterolemia and statin intolerance. The proportion of the study population with type 2 diabetes was ∼24%. After the 24 weeks, alirocumab lowered LDL cholesterol levels by 54.8% compared with 20.1% with ezetimibe. Although there were similar rates of any adverse event for all treatments, there were fewer events that led to treatment discontinuation for alirocumab (18.3% vs. 25.0% for ezetimibe and 25.4% for atorvastatin) as well as fewer skeletal muscle–related adverse events (32.5% vs. 41.1% with ezetimibe and 46% with atorvastatin) (126). Individuals in all treatment arms were offered the opportunity of an open-label extension phase, in which all received alirocumab for ∼3 years. LDL cholesterol reductions of more than 50% were either achieved or maintained for the 281 individuals who either continued with or switched to alirocumab for the extension phase, and these reductions were sustained throughout the treatment period (127).

Evolocumab was evaluated for its safety and efficacy in people with statin intolerance in the Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 1, 2, and 3 (GAUSS 1, 2, and 3) trials as well as the OSLER open-label extension of the GAUSS 1 and 2 trials. There were 160 and 307 individuals in the GAUSS 1 and 2 trials, respectively, who were randomized to various doses of evolocumab plus ezetimibe 10 mg or ezetimibe 10 mg plus placebo injection for 12 weeks. Reductions in LDL cholesterol ranged from 41% to 63% (depending on the dose) for evolocumab/ezetimibe compared with 15% to 18% for ezetimibe/placebo. Similar to what was found in the alirocumab studies, musculoskeletal adverse effects occurred in fewer of those treated with evolocumab/ezetimibe than with ezetimibe/placebo, although rates of discontinuation were similar (5% and 6%, respectively) due to these effects. Use of low-dose statins was allowed in these studies and was associated with an increase in the incidence of musculoskeletal adverse effects (128,129). One hundred twenty-eight individuals from the GAUSS 1 trial were rerandomized to evolocumab (420 mg monthly) plus standard of care compared with the standard of care for 1 year, and then all participants were treated with 420 mg of evolocumab monthly plus standard of care. Two hundred fifty-four individuals were rerandomized into two dosing options of evolocumab (140 mg biweekly or 420 mg monthly) compared with standard of care for 1 year, and then all were continued on 420 mg monthly for an additional year. After 1 year, the LDL cholesterol was reduced from baseline (beginning of the GAUSS 1 or 2 trial) by a mean of 57% in those treated with evolocumab compared with 13% with the standard of care, with a 59% reduction (from baseline) by the end of year 2. Fourteen percent of participants in the extension trials experienced musculoskeletal adverse effects; however, these effects did not lead to any participant discontinuing the trials (130). Similar LDL cholesterol reductions were demonstrated in the GAUSS 3 trial after 24 weeks (−54.5% with evolocumab compared with –16.7% with ezetimibe), with slightly higher rates of musculoskeletal adverse events (20.7% with evolocumab and 28.8% with ezetimibe). The higher rates of these adverse events may be due in part to the first phase of this trial, which randomized individuals to a statin rechallenge with either atorvastatin or placebo (131).

Inclisiran has also been proposed as an option for individuals with statin intolerance. Although most individuals (90–95%) in the later ORION-10 and ORION-11 trials were on statin therapy (123), the Trial to Evaluate the Effect of ALN-PCSSC Treatment on Low-density Lipoprotein Cholesterol (ORION-1) included individuals with documented statin intolerance. The percentages of individuals not taking statins were 26% of the 253 who received either a single injection of inclisiran or placebo and 28% of the 248 who received two injections of inclisiran or placebo. Both groups were followed for 1 year to assess the durability of the initial (30–45%, dose-dependent) lowering of LDL cholesterol. Almost all individuals treated with inclisiran maintained their LDL cholesterol levels at 180 days; however, the levels returned to within 20% change from the baseline for 17–52% of individuals, and response depended on both the number and strength of the inclisiran dose(s) received (132). A proportion of these individuals continued into the open-label Extension Trial of Inclisiran in Participants With Cardiovascular Disease and High Cholesterol (ORION-3), in which they returned to inclisiran 300 mg given every 6 months and were compared with individuals given placebo in ORION-1 and those who were given evolocumab 140 mg every 2 weeks for 1 year and then transitioned to inclisiran. The change in LDL cholesterol levels was compared with the baseline, which was defined as the baseline for the ORION-1 trial for those initially treated with inclisiran (as they were inclisarin naive at that point) or the start of the ORION-3 trial for those previously treated with placebo. It is important to note that of the ORION-3 participants, only 23% had diabetes and 33% were not taking statin therapy. Both arms maintained an LDL cholesterol reduction of ~45% through the end of year 4 (133). The significant response was seen across the groups during the ORION-1 trial and in the ORION-3 extension, and it may be expected that those with statin intolerance experienced a response similar to the response of those on statin therapy; however, evaluation of response based on background lipid-lowering therapy was not described.

Bempedoic Acid

Bempedoic acid is a novel LDL cholesterol–lowering agent that is indicated as an adjunct to diet and maximum tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL cholesterol. A pooled analysis suggests that bempedoic acid therapy lowers LDL cholesterol levels by about 23% compared with placebo (134). This agent should be considered for individuals who cannot use or tolerate other evidence-based LDL cholesterol–lowering approaches or for whom those other therapies are inadequately effective (135). The Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid or Placebo (CLEAR Outcomes) trial evaluated the impact of bempedoic acid on cardiovascular events for individuals with established ASCVD (70% of population) or at high risk for ASCVD (30% of population) and considered to be intolerant to statin therapy. It is important to note that ~19% of individuals were on very-low-dose statin therapy at baseline. Bempedoic acid was found to reduce the composite outcome of four-point major adverse cardiovascular events by 13% compared with placebo (136) The HR for the primary outcome was more reduced in the primary prevention group (HR 0.68 [95% CI 0.53–0.87]) compared with the secondary prevention group of individuals with established cardiovascular disease (HR 0.91 [95% CI 0.81–1.01]). In addition, in a preplanned subanalysis of the primary prevention population, the use of bempedoic acid resulted in a 30% reduction in primary composite outcome compared with placebo (137).

Treatment of Other Lipoprotein Fractions or Targets

Recommendations

10.29 For individuals with fasting triglyceride levels ≥500 mg/dL (≥5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**

10.30 In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL [2.0–5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism), and medications that raise triglycerides. **C**

10.31 In individuals with ASCVD or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL [1.5–5.6 mmol/L]), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **A**

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol (138). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL and especially >1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see STATIN TREATMENT). In people with moderate hypertriglyceridemia, lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) enrolled 8,179 adults receiving statin therapy with moderately elevated triglycerides (135–499 mg/dL, median baseline of 216 mg/dL) who had either established cardiovascular disease (secondary prevention cohort) or diabetes plus at least one other cardiovascular risk factor (primary prevention cohort) (139). Individuals were randomized to icosapent ethyl 4 g/day (2 g twice daily with food) versus placebo. The trial met its primary end point, demonstrating a 25% relative risk reduction ($P < 0.001$) for the primary end point composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. This risk reduction was seen in people with or without diabetes at baseline. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 26% ($P < 0.001$). Additional ischemic end points were significantly lower in the icosapent ethyl group than in the placebo group, including cardiovascular death, which was reduced by 20% ($P = 0.03$). The proportions of individuals experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking for other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (139). As an example, the addition of 4 g per day of a carboxylic acid formulation of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3 carboxylic acid) to statin therapy in individuals with atherogenic dyslipidemia and high cardiovascular risk, 70% of whom had diabetes, did not reduce the risk of major adverse cardiovascular events compared with the inert comparator of corn oil (140).

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (141). In a large trial in people with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (142).

Other Combination Therapy

Recommendations

10.32 Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. **A**

10.33 Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

Statin and Fibrate Combination Therapy

Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (143).

In the ACCORD study, in people with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL (≥2.3 mmol/L) and an HDL cholesterol level ≤34 mg/dL (≤0.9 mmol/L) (144).

Statin and Niacin Combination Therapy

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 people (about one-third with diabetes) with established ASCVD, LDL cholesterol levels <180 mg/dL (<4.7 mmol/L), low HDL cholesterol levels (men <40 mg/dL [<1.0 mmol/L] and women <50 mg/dL [<1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (145).

The much larger Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also failed to show a benefit of adding niacin to background statin therapy (146). A total of 25,673 individuals with prior vascular disease were randomized to receive 2 g of extended-release niacin and 40 mg of laropiprant (an antagonist of the prostaglandin D2 receptor DP1 that has been shown to improve participation in niacin therapy) versus a matching placebo daily and followed for a median follow-up period of 3.9 years. There was no significant difference in the rate of coronary death, MI, stroke, or coronary revascularization with the addition of niacin–laropiprant versus placebo (13.2% vs. 13.7%; rate ratio 0.96; $P = 0.29$). Niacin–laropiprant was associated with an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points; $P < 0.001$) and disturbances in diabetes management among those with diabetes. In addition, there was an increase in serious adverse events associated with the gastrointestinal system, musculoskeletal system, skin, and, unexpectedly, infection and bleeding.

Therefore, combination therapy with a statin and niacin is not recommended, given the lack of efficacy on major ASCVD outcomes and increased side effects.

Diabetes Risk With Statin Use

Several studies have reported a modestly increased risk of incident type 2 diabetes with statin use (147,148), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes, even for individuals at highest risk for diabetes (149). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (149). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 individuals with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 individuals (148).

Lipid-Lowering Agents and Cognitive Function

Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised, several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (150). First, there are three large randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen between statin and placebo (151–154). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (112) or PCSK9 inhibitors (115,155) to statin therapy, including among individuals treated to very low LDL cholesterol levels. In addition, the most recent systematic review of the U.S. Food and Drug Administration's (FDA's) postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in individuals receiving statins found that published data do not reveal an adverse effect of statins on cognition (156). Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (156).

ANTIPLATELET AGENTS

Recommendations

10.34 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. **A**

10.35a For individuals with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
10.35b The length of treatment with dual antiplatelet therapy using low-dose aspirin and a P2Y12 inhibitor in individuals with diabetes after an acute coronary syndrome or acute ischemic stroke/transient ischemic attack should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, respectively. **E**
10.36 Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease (PAD) and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**
10.37 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the individual on the benefits versus the comparable increased risk of bleeding. **A**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk individuals with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among individuals with no previous cardiovascular events, its net benefit is more controversial (147,157).

Previous randomized controlled trials of aspirin, specifically in people with diabetes, failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (158–160).

The Antithrombotic Trialists' Collaboration published an individual patient–level meta-analysis (161) of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (relative risk 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (relative risk 0.95 [95% CI 0.78–1.15]) or total stroke.

Most recently, the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized 15,480 people with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo (162). The primary efficacy end point was vascular death, MI, stroke, or transient ischemic attack. The primary safety outcome was major bleeding (i.e., intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal bleeding, or other serious bleeding). During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy end point (8.5% vs. 9.6%; $P = 0.01$). In contrast, major bleeding was significantly increased from 3.2 to 4.1% in the aspirin group (rate ratio 1.29; $P = 0.003$), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There were no significant differences by sex, weight, or duration of diabetes or other baseline factors, including ASCVD risk score.

Two other large, randomized trials of aspirin for primary prevention, in people without diabetes (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (163) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (164), which included 11% with diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 individuals over a period of 60 months of follow-up, the primary end point occurred in 4.29% vs. 4.48% of individuals in the aspirin versus placebo groups (HR 0.96 [95% CI 0.81–1.13]; $P = 0.60$). Gastrointestinal bleeding events (characterized as mild) occurred in 0.97% of individuals in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36–3.28]; $P = 0.0007$). In ASPREE, including 19,114 individuals, for cardiovascular disease (fatal CHD, MI, stroke, or hospitalization for heart failure) after a median of 4.7 years of follow-up, the rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]). The rate of major hemorrhage per 1,000 person-years was 8.6 events vs. 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62]; $P < 0.001$).

Thus, aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. However, for adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (165).

Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, or renal disease) (166–169). Noninvasive imaging techniques such as coronary calcium scoring may help further tailor aspirin therapy, particularly in those at low risk (170,171). For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit (162,164). Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.

For people with documented ASCVD, use of aspirin for secondary prevention has far greater benefit than risk; for this indication, aspirin is still recommended (157).

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors), as the low benefit is likely to be outweighed by the risk of bleeding. Clinical judgment should be used for those at intermediate risk (younger individuals with one or more risk factors or older individuals with no risk factors) until further research is available. Individuals' willingness to undergo long-term aspirin therapy should also be considered in shared decision-making (172).

Aspirin use in individuals aged $<$21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving people with diabetes ranged from 50 to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dose may help to reduce side effects (173). In the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial of individuals with established cardiovascular disease, 38% of whom had diabetes, there were no significant differences in cardiovascular events or major bleeding between individuals assigned to 81 mg and those assigned to 325 mg of aspirin daily (174). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from people with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in people with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus are not sensitive to the effects of aspirin (175). “Aspirin resistance” has been described in people with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry and measurement of thromboxane B_2) (176), but other studies suggest no impairment in aspirin response among people with diabetes (177). A trial suggested that more frequent dosing of aspirin may reduce platelet reactivity in individuals with diabetes (178); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. Another meta-analysis raised the hypothesis that low-dose aspirin efficacy is reduced in those weighing $>$70 kg (179); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would thus not validate this suggested hypothesis (162). It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Receptor Antagonist Use

Combination dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist is indicated after acute coronary syndromes and coronary revascularization with stenting (180). In addition, current guidelines recommend short-term dual antiplatelet therapy after high-risk transient ischemic attack and minor stroke (181). The indications for dual antiplatelet therapy and length of treatment are rapidly evolving and should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, respectively. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (182). In people with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events, including cardiovascular and CHD death (183). Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in people with diabetes and stable coronary artery disease (184,185). However, a higher incidence of major bleeding, including intracranial hemorrhage, was noted with dual antiplatelet therapy. The net clinical benefit (ischemic benefit vs. bleeding risk) was improved with ticagrelor therapy in the large prespecified subgroup of individuals with history of percutaneous coronary intervention, while no net benefit was seen in individuals without prior percutaneous coronary intervention (185). However, early aspirin discontinuation compared with continued dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risks of mortality and ischemic events, as shown in a prespecified analysis of people with diabetes enrolled in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial and a recent meta-analysis (186,187).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low-dose rivaroxaban may be considered for people with stable coronary and/or PAD to prevent major adverse limb and cardiovascular complications. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial of 27,395 individuals with established coronary artery disease and/or PAD, aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus placebo in the reduction of cardiovascular ischemic events, including major adverse limb events. The absolute benefits of combination therapy appeared larger in people with diabetes, who comprised 10,341 of the trial participants (188,189). A similar treatment strategy was evaluated in the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial (190), in which 6,564 individuals with PAD who had undergone revascularization were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin or placebo plus aspirin. Rivaroxaban treatment in this group of individuals was also associated with a significantly lower incidence of ischemic cardiovascular events, including major adverse limb events. However, an increased risk of major bleeding was noted with rivaroxaban added to aspirin treatment in both COMPASS and VOYAGER PAD.

The risks and benefits of dual antiplatelet or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible individuals, and shared decision-making should be used to determine an individually appropriate treatment approach. This field of cardiovascular risk reduction is evolving rapidly, as are the definitions of optimal care for individuals with differing types and circumstances of cardiovascular complications.

CARDIOVASCULAR DISEASE

Screening

Recommendations

10.38a In asymptomatic individuals, routine screening for coronary artery disease is not recommended, as it does not improve outcomes as long as ASCVD risk factors are treated. **A**

10.38b Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms; signs or symptoms of associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or PAD; or electrocardiogram abnormalities (e.g., Q waves). **E**

10.39a Adults with diabetes are at increased risk for the development

of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure. Consider screening adults with diabetes by measuring a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) to facilitate prevention of stage C heart failure. B
10.39b In asymptomatic individuals with diabetes and abnormal natriuretic peptide levels, echocardiography is recommended to identify stage B heart failure. A
10.40 In asymptomatic individuals with diabetes and age ≥50 years, microvascular disease in any location, or foot complications or any end-organ damage from diabetes, screening for PAD with ankle-brachial index testing is recommended to guide treatment for cardiovascular disease prevention and limb preservation. A In individuals with diabetes duration ≥10 years, screening for PAD should be considered. B

Treatment

Recommendations

10.41 Among people with type 2 diabetes who have established ASCVD or established kidney disease, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated cardiovascular disease benefit (**Table 10.3*B*** and **Table 10.3*C***) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering treatment plans. A
10.41a In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. A
10.41b In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a GLP-1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. A
10.41c In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, combined therapy with an SGLT2 inhibitor with demonstrated cardiovascular benefit and a GLP-1 receptor agonist with demonstrated cardiovascular benefit may be considered for additive reduction of the risk of adverse cardiovascular and kidney events. A
10.42a In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, an SGLT2 inhibitor (including SGLT1/2 inhibitor) with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure and cardiovascular death. A
10.42b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, an SGLT2 inhibitor with proven benefit in this patient population is recommended to improve symptoms, physical limitations, and quality of life. A
10.43 For individuals with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, addition of finerenone is recommended to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. A
10.44 In individuals with diabetes with established ASCVD or aged ≥55 years with additional cardiovascular risk factors, ACE inhibitor or ARB therapy is recommended to reduce the risk of cardiovascular events and mortality. A
10.45a In individuals with diabetes and asymptomatic stage B heart failure, an interprofessional approach to optimize guideline-directed medical therapy, which should include a cardiovascular disease specialist, is recommended to reduce the risk for progression to symptomatic (stage C) heart failure. A
10.45b In individuals with diabetes and asymptomatic stage B heart failure, ACE inhibitors/ARBs and β-blockers are recommended to reduce the risk for progression to symptomatic (stage C) heart failure. A
10.45c In individuals with type 2 diabetes and asymptomatic stage B heart failure or with high risk of or established cardiovascular disease, treatment with an SGLT inhibitor (including SGLT2 or SGLT1/2 inhibitors) is recommended to reduce the risk of hospitalization for heart failure. A
10.45d In individuals with type 2 diabetes and diabetic kidney disease, finerenone is recommended to reduce the risk of hospitalization for heart failure. A
10.45e In individuals with diabetes, guideline-directed medical therapy for myocardial infarction and symptomatic stage C heart failure is recommended with ACE inhibitors/ARBs, MRAs, angiotensin receptor/neprilysin inhibitor, β-blockers, and SGLT2 inhibitors, similar to guideline-directed medical therapy for people without diabetes. A
10.46 In people with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains >30 mL/min/1.73 m^2 but should be avoided in unstable or hospitalized individuals with heart failure. B
10.47 Individuals with type 1 diabetes and those with type 2 diabetes who are ketosis prone and/or those consuming ketogenic diets who are treated with SGLT inhibition should be educated on the risks and signs of ketoacidosis and methods of risk management and provided with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate). E

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should

Table 10.3*A*—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors

	SAVOR-TIMI 53 (289) (*n* = 16,492)	EXAMINE (311) (*n* = 5,380)	TECOS (291) (*n* = 14,671)	CARMELINA (292,312) (*n* = 6,979)	CAROLINA (246) (*n* = 6,042)
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Linagliptin/placebo	Linagliptin/glimepiride
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and high CV and renal risk	Type 2 diabetes and high CV risk
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	6.5–10.0	6.5–8.5
Age (years)*	65.1	61.0	65.4	65.8	64.0
Race (% White)	75.2	72.7	67.9	80.2	73.0
Sex (% male)	66.9	67.9	70.7	62.9	60.0
Diabetes duration (years)*	10.3	7.1	11.6	14.7	6.2
Median follow-up (years)	2.1	1.5	3.0	2.2	6.3
Statin use (%)	78	91	80	71.8	64.1
Metformin use (%)	70	66	82	54.8	82.5
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8	34.5/4.5
Mean baseline A1C (%)	8.0	8.0	7.2	7.9	7.2
Mean difference in A1C between groups at end of treatment (%)	−0.3†	−0.3†	−0.3†	−0.36†	0
Year started/ reported	2010/2013	2009/2013	2008/2015	2013/2018	2010/2019
Primary outcome‡	3-point MACE 1.00 (0.89–1.12)	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.98 (0.89–1.08)	3-point MACE 1.02 (0.89–1.17)	3-point MACE 0.98 (0.84–1.14)
Key secondary outcome‡	Expanded MACE 1.02 (0.94–1.11)	4-point MACE 0.95 (95% UL ≤1.14)	3-point MACE 0.99 (0.89–1.10)	Kidney composite (ESRD, sustained ≥40% decrease in eGFR, or renal death) 1.04 (0.89–1.22)	4-point MACE 0.99 (0.86–1.14)
Cardiovascular death‡	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)
MI‡	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.12 (0.90–1.40)	1.03 (0.82–1.29)
Stroke‡	1.11 (0.88–1.39)	0.91 (0.55–1.50)	0.97 (0.79–1.19)	0.91 (0.67–1.23)	0.86 (0.66–1.12)
HF hospitalization‡	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.90 (0.74–1.08)	1.21 (0.92–1.59)
Unstable angina hospitalization‡	1.19 (0.89–1.60)	0.90 (0.60–1.37)	0.90 (0.70–1.16)	0.87 (0.57–1.31)	1.07 (0.74–1.54)
All-cause mortality‡	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.98 (0.84–1.13)	0.91 (0.78–1.06)
Worsening nephropathy‡§	1.08 (0.88–1.32)	—	—	Kidney composite (see above)	—

—, not assessed/reported; ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; UL, upper limit. Data in this table were adapted from Cefalu et al. (313). *Age was reported as means in all trials except EXAMINE, which reported medians; diabetes duration was reported as means in all trials except SAVOR-TIMI 53 and EXAMINE, which reported medians. †Significant difference in A1C between groups ($P < 0.05$). ‡Outcomes reported as hazard ratio (95% CI). §Worsening nephropathy is defined as a doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (>530 mmol/L) in SAVOR-TIMI 53. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53.

undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Individuals for Atherosclerotic Cardiovascular Disease

The screening of asymptomatic individuals with high ASCVD risk is not recommended (191), in part because these high-risk people should already be receiving intensive medical therapy—an approach that provides benefits similar to those of invasive revascularization (192,193). There is also some evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (194). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in people with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (195–197). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic people with type 2 diabetes and normal ECGs (198). Despite abnormal myocardial perfusion imaging in more than one in five individuals, cardiac outcomes were essentially equal (and very low) in screened versus unscreened individuals. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which people with type 2 diabetes will have silent ischemia on screening tests (199,200).

Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes, though research is ongoing. Since asymptomatic people with diabetes with higher coronary disease burden have more future cardiac events (195,201,202), these additional imaging tests may provide reasoning for treatment intensification and/or guide informed individual decision-making and willingness for medication initiation and participation.

While coronary artery screening methods, such as calcium scoring, may improve cardiovascular risk assessment in people with type 2 diabetes (203), their routine use leads to radiation exposure and may result in unnecessary invasive testing, such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risk of such an approach in asymptomatic individuals remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Screening for Asymptomatic Heart Failure in People With Diabetes

People with diabetes are at an increased risk for developing heart failure, as shown in multiple longitudinal, observational studies (9,204–206). This association is not only observed in people with type 2 diabetes but also evident in people with type 1 diabetes (9,207,208). In a large multinational cohort of 750,000 people with diabetes without established cardiovascular disease, heart failure and CKD were the most frequent first cardiovascular disease manifestations (209). For a detailed review of screening, diagnosis, and treatment recommendations of heart failure in people with diabetes, the reader is further referred to the ADA consensus report "Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association" (7).

The increased risk for heart failure in people with diabetes is classified as the presence of stage A heart failure, i.e., an increased risk for heart failure but without symptoms, structural heart disease, or biomarker evidence of myocardial strain (210). Similar to those with stage A heart failure, people with stage B heart failure are asymptomatic but have evidence of structural heart disease or functional cardiac abnormalities, including elevated biomarkers of myocardial strain or increased filling pressures. During these asymptomatic stages of heart failure, people with diabetes are at particularly high risk for progression to symptomatic stage C and D heart failure (211,212).

Identification, risk stratification, and early treatment of risk factors in people with diabetes and asymptomatic stages of heart failure reduce the risk for progression to symptomatic heart failure (213, 214). In people with type 2 diabetes, measurement of natriuretic peptides, including B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), identifies people at risk for heart failure development, progression of symptoms, and heart failure–related mortality. For example, in the Canagliflozin Cardiovascular Assessment Study (CANVAS), a baseline NT-proBNP level $\geq$125 pg/mL predicted heart failure hospitalization and all-cause mortality (215). In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, increased baseline NT-proBNP levels or an increase after a repeated measurement at 6 months was associated with an increased risk for symptomatic heart failure (216). In a combined analysis of three cohorts without disease (Atherosclerosis Risk In Communities [ARIC], Dallas Heart Study, and Multi-Ethnic Study of Atherosclerosis [MESA]), including 33% of participants with diabetes and 66% with prediabetes, biomarker screening stratifies people at high risk for incident heart failure (217). A similar association and prognostic values of increased NT-proBNP with increased cardiovascular and all-cause mortality has been reported in people with type 1 diabetes (218).

Results from several randomized controlled trials revealed that more intensive treatment of risk factors in people with increased levels of natriuretic peptides reduces the risk for symptomatic heart failure, heart failure hospitalization, and newly diagnosed left ventricular dysfunction. The NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients (PONTIAC) trial enrolled 300 people with type 2 diabetes and elevated NT-proBNP levels to usual diabetes care versus usual diabetes care plus intensified risk factor treatment in cardiac outpatient clinics (214). After 12 months, there was significant increased use of renin-angiotensin system antagonists and β-blockers in the intensive treatment group but no difference in blood pressure. The primary outcome of hospitalization or death due to cardiac disease was significantly reduced in the intensive treatment group (HR 0.35 [95% CI 0.13–0.98]; *P* = 0.044). The St Vincent's Screening to Prevent Heart Failure Study (STOP-HF) was a randomized controlled trial that enrolled 1,374 participants with cardiovascular risk factors to receive either usual primary care or screening with BNP testing. Participants with an elevated BNP level of 50 pg/mL or higher underwent echocardiography followed by collaborative care between primary care

Table 10.3*B*—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists

	ELIXA (260) (*n* = 6,068)	LEADER (255) (*n* = 9,340)	SUSTAIN-6 (256)* (*n* = 3,297)	EXSCEL (261) (*n* = 14,752)	REWIND (259) (*n* = 9,901)	PIONEER-6 (257) (*n* = 3,183)
Intervention	Lixisenatide/placebo	Liraglutide/placebo	Semaglutide s.c. injection/placebo	Exenatide QW/placebo	Dulaglutide/placebo	Semaglutide oral/placebo
Main inclusion criteria	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and prior ASCVD event or risk factors for ASCVD	Type 2 diabetes and high CV risk (age of ≥50 years with established CVD or CKD, or age of ≥60 years with CV risk factors only)
A1C inclusion criteria (%)	5.5–11.0	≥7.0	≥7.0	6.5–10.0	≤9.5	None
Age (years)†	60.3	64.3	64.6	62	66.2	66
Race (% White)	75.2	77.5	83.0	75.8	75.7	72.3
Sex (% male)	69.3	64.3	60.7	62	53.7	68.4
Diabetes duration (years)†	9.3	12.8	13.9	12	10.5	14.9
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Statin use (%)	93	72	73	74	66	85.2 (all lipid-lowering)
Metformin use (%)	66	76	73	77	81	77.4
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2	32/9	84.7/12.2
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4	8.2
Mean difference in A1C between groups at end of treatment (%)	−0.3‡^	−0.4‡	−0.7 or −1.0^	−0.53‡^	−0.61‡	−0.7
Year started/reported	2010/2015	2010/2016	2013/2016	2010/2017	2011/2019	2017/2019
Primary outcome§	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)	3-point MACE 0.74 (0.58–0.95)	3-point MACE 0.91 (0.83–1.00)	3-point MACE 0.88 (0.79–0.99)	3-point MACE 0.79 (0.57–1.11)

Continued on p. S199

Table 10.3*B*—Continued

	ELIXA (260) (n = 6,068)	LEADER (255) (n = 9,340)	SUSTAIN-6 (256)* (n = 3,297)	EXSCEL (261) (n = 14,752)	REWIND (259) (n = 9,901)	PIONEER-6 (257) (n = 3,183)
Key secondary outcome§	Expanded MACE 1.02 (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)	Expanded MACE 0.74 (0.62–0.89)	Individual components of MACE (see below)	Composite microvascular outcome (eye or renal outcome) 0.87 (0.79–0.95)	Expanded MACE or HF hospitalization 0.82 (0.61–1.10)
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	1.18 (0.73–1.90)
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	1.14 (0.84–1.54)	1.56 (0.60–4.01)
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
Worsening nephropathy§‖	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.85 (0.77–0.93)	—

—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. Data in this table were adapted from Cefalu et al. (313). *Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians. ‡Significant difference in A1C between groups ($P < 0.05$). ^A1C change of 0.66% with 0.5 mg and 1.05% with 1-mg dose of semaglutide. §Outcomes reported as hazard ratio (95% CI). ‖Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of <45 mL/min/1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND.

physicians and cardiovascular specialist services. Participants in the intervention group received more renin-angiotensin/aldosterone system–based therapy. The primary end point of left ventricular dysfunction and heart failure was significantly reduced in the intervention group (odds ratio 0.55 [95% CI 0.37–0.82]; $P = 0.003$). The risk for left ventricular systolic dysfunction, diastolic dysfunction, or heart failure was significantly reduced in the BNP-guided intervention group. Approximately 18% of people in the control and intervention groups had a diagnosis of diabetes. Finally, in the original Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno-2) trial, 160 individuals with type 2 diabetes and microalbuminuria were enrolled, and the trial examined the effect of multifactorial treatment on cardiovascular outcomes (219). When stratified in a later analysis by NT-proBNP levels, plasma NT-proBNP levels above the median were associated with increased risk of cardiovascular disease, and a decrease in plasma NT-proBNP of 10 pg/mL for the first 2 years of intervention was associated with a 1% relative risk reduction in the primary cardiovascular end point (220).

Based on this collective evidence, the committee recommends considering screening asymptomatic adults with diabetes for the development of cardiac structural or functional abnormalities (stage B heart failure) by measurement of natriuretic peptides, including BNP or NT-proBNP levels. The biomarker threshold for abnormal values is a BNP level ≥50 pg/mL and NT-proBNP ≥125 pg/mL. Abnormal levels of natriuretic peptide will need to be evaluated in the context of each individual, using clinical judgment, and in the absence of any possible competing diagnoses, particularly recognizing conditions that may lead to increased levels of natriuretic peptide, including renal insufficiency, pulmonary disease including pulmonary hypertension and chronic obstructive lung disease, obstructive sleep apnea, ischemic and hemorrhagic stroke, and anemia. Conversely, natriuretic peptide levels may be decreased in the population with obesity, which impairs sensitivity of testing.

Risk stratification for incident heart failure (stage A) and identification of people with asymptomatic cardiac abnormalities

Table 10.3C—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

	EMPA-REG OUTCOME (11) (*n* = 7,020)	CANVAS Program (12) (*n* = 10,142)	DECLARE-TIMI 58 (249) (*n* = 17,160)	CREDENCE (247) (*n* = 4,401)	DAPA-CKD (250,314) (*n* = 4,304; 2,906 with diabetes)	VERTIS CV (254,315) (*n* = 8,246)	DAPA-HF (14) (*n* = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (253) (*n* = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (242,316) (*n* = 5,988; 2,938 with diabetes)	DELIVER (252) (*n* = 6,263; 2,807 with diabetes)
Intervention	Empagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Ertugliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo*	Empagliflozin/placebo	Dapagliflozin/placebo
Main inclusion criteria	Type 2 diabetes and preexisting CVD	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 CV risk factors at ≥50 years of age	Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD	Type 2 diabetes and albuminuric kidney disease	Albuminuric kidney disease, with or without diabetes	Type 2 diabetes and ASCVD	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction >40%	NYHA class II, III, or IV heart failure and an ejection fraction >40% with or without diabetes
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5	≥6.5	6.5–12	—	7.0–10.5	—	—	—	—
Age (years)†	63.1	63.3	64.0	63	61.8	64.4	66	67.2, 66.5	71.8, 71.9	71.7
Race (% White)	72.4	78.3	79.6	66.6	53.2	87.8	70.3	71.1, 69.8	76.3, 75.4	71.2
Sex (% male)	71.5	64.2	62.6	66.1	66.9	70	76.6	76.5, 75.6	55.4, 55.3	56.1
Diabetes duration (years)†	57% >10	13.5	11.0	15.8	—	12.9	—	—	—	—
Median follow-up (years)	3.1	3.6	4.2	2.6	2.4	3.5	1.5	1.3	2.2	2.3
Statin use (%)	77	75	75 (statin or ezetimibe use)	69	64.9	—	—	—	68.1, 68.8	—
Metformin use (%)	74	77	82	57.8	29	—	51.2% (of people with diabetes)	—	—	—
Prior CVD/CHF (%)	99/10	65.6/14.4	40/10	50.4/14.8	37.4/10.9	99.9/23.1	100% with CHF	100% with CHF	100% with CHF	100% with CHF
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	7.1% (7.8% in those with diabetes)	8.2	—	—	—	6.6
Mean difference in A1C between groups at end of treatment (%)	−0.3^	−0.58‡	−0.43‡	−0.31	—	−0.48 to −0.5	—	—	—	—
Year started/reported	2010/2015	2009/2017	2013/2018	2017/2019	2017/2020	2013/2020	2017/2019	2017/2020	2017/2020	2018/2022

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Table 10.3C—Continued

	EMPA-REG OUTCOME (11) (*n* = 7,020)	CANVAS Program (12) (*n* = 10,142)	DECLARE-TIMI 58 (249) (*n* = 17,160)	CREDENCE (247) (*n* = 4,401)	DAPA-CKD (250,314) (*n* = 4,304; 2,906 with diabetes)	VERTIS CV (254,315) (*n* = 8,246)	DAPA-HF (14) (*n* = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (253) (*n* = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (242,316) (*n* = 5,988; 2,938 with diabetes)	DELIVER (252) (*n* = 6,263; 2,807 with diabetes)
Primary outcome§	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)	3-point MACE 0.93 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)	ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82)	≥50% decline in eGFR, ESKD, or death from renal or CV cause 0.61 (0.51–0.72)	3-point MACE 0.97 (0.85–1.11)	Worsening heart failure or death from CV causes 0.74 (0.65–0.85) Results did not differ by diabetes status	CV death or HF hospitalization 0.75 (0.65–0.86)	CV death or HF hospitalization 0.79 (0.69–0.90)	Worsening HF or CV death 0.82 (0.73–0.92)
Key secondary outcome§	4-point MACE 0.89 (0.78–1.01)	All-cause and CV mortality (see below)	Death from any cause 0.93 (0.82–1.04) Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95)	≥50% decline in eGFR, ESKD, or death from renal cause 0.56 (0.45–0.68) CV death or HF hospitalization 0.71 (0.55–0.92) Death from any cause 0.69 (0.53–0.88)	CV death or HF hospitalization 0.88 (0.75–1.03) CV death 0.92 (0.77–1.11) Renal death, renal replacement therapy, or doubling of creatinine 0.81 (0.63–1.04)	CV death or HF hospitalization 0.75 (0.65–0.85)	Total HF hospitalizations 0.70 (0.58–0.85) Mean slope of change in eGFR 1.73 (1.10–2.37)	All HF hospitalizations (first and recurrent) 0.73 (0.61–0.88) Rate of decline in eGFR (−1.25 vs. −2.62 mL/min/1.73 m^2; $P < 0.001$)	Total number worsening HF and CV deaths 0.77 (0.67–0.89) Change in KCCQ TSS at month 8 1.11 (1.03–1.21) Mean change in KCCQ TSS 2.4 (1.5–3.4) All-cause mortality 0.94 (0.83–1.07)
Cardiovascular death§	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.92 (0.77–1.11)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.91 (0.76–1.09)	0.88 (0.74–1.05)
MI§	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	—	—	1.04 (0.86–1.26)	—	—	—	—
Stroke§	1.18 (0.89–1.56)	0.87 (0.69–1.09)	1.01 (0.84–1.21)	—	—	1.06 (0.82–1.37)	—	—	—	—
HF hospitalization§	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	—	0.70 (0.54–0.90)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.77 (0.67–0.89)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—	—	—	—	—	—	—	—	—
All-cause mortality§	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.93 (0.80–1.08)	0.83 (0.71–0.97)	0.92 (0.77–1.10)	1.00 (0.87–1.15)	0.94 (0.83–1.07)
Worsening nephropathy§‖	0.61 (0.53–0.70)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	(See primary outcome)	(See primary outcome)	(See secondary outcomes)	0.71 (0.44–1.16)	Composite renal outcome 0.50 (0.32–0.77)	Composite renal outcome** 0.95 (0.73–1.24)	—

—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYHA, New York Heart Association. Data in this table were adapted from Cefalu et al. (313). *Baseline characteristics for EMPEROR-Reduced displayed as empagliflozin, placebo. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EMPA-REG OUTCOME, which reported as percentage of population with diabetes duration >10 years, and DECLARE-TIMI 58, which reported median. ‡Significant difference in A1C between groups ($P < 0.05$). ^AIC change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as hazard ratio (95% CI). ‖Definitions of worsening nephropathy differed between trials. **Composite outcome in EMPEROR-Preserved: time to first occurrence of chronic dialysis, renal transplantation; sustained reduction of ≥40% in eGFR, sustained eGFR <15 mL/min/1.73 m^2 for individuals with baseline eGFR ≥30 mL/min/1.73 m^2.

(stage B) may prevent progression to the symptomatic stages of heart failure (stages C and D). People with diabetes and an elevated natriuretic peptide level without any symptoms of heart failure should be considered to have stage B heart failure, as there is evidence for increased filling pressure and wall strain. In people with diabetes and an abnormal natriuretic peptide level, echocardiography is recommended as the next step to screen for structural heart disease and echocardiographic Doppler indices for evidence of diastolic dysfunction and increased filling pressures (221). At this stage, an interprofessional approach, which should include a cardiovascular disease specialist, is recommended to implement a guideline-directed medical treatment strategy, which may reduce the risk of progression to symptomatic stages of heart failure (213). The recommendations for screening and treatment of heart failure in people with diabetes discussed in this section are consistent with the ADA consensus report on heart failure (7) and with current American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure (210).

Screening for Asymptomatic Peripheral Artery Disease in People With Diabetes

The risk for PAD in people with diabetes is higher than that in people without diabetes (222–224). In the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, 30% of people aged 50–69 years with a history of cigarette smoking or diabetes, or aged ≥70 years regardless of risk factors, had PAD (225). Similarly, in other screening studies, 26% of people with diabetes have been shown to have PAD (226), and diabetes increased the odds of having PAD by 85% (227). Notably, classical symptoms of claudication are uncommon, and almost half of people with newly diagnosed PAD were asymptomatic (225). Conversely, up to two-thirds of people with asymptomatic PAD have been shown to have comorbid diabetes (228). Risk factors associated with an increased risk for PAD in people with diabetes include age, smoking, hypertension, dyslipidemia, worse glycemic control, longer duration of diabetes, neuropathy, and retinopathy as well as a prior history of cardiovascular disease (229,230). In addition, the presence of microvascular disease is associated with adverse outcomes in people with PAD, including an increased risk for future limb amputation (231,232).

Screening for asymptomatic PAD may lead to early detection and treatment strategies to reduce the risk for progression of PAD and limb preservation. In addition, secondary prevention of PAD has been shown to reduce adverse cardiovascular and limb outcomes. While a positive screening test for PAD in an asymptomatic population has been associated with increased cardiovascular event rates (233,234), prospective, randomized studies addressing whether screening for PAD in people with diabetes improves long-term limb outcomes and cardiovascular event rates are limited. In the randomized controlled Viborg Vascular (VIVA) trial, 50,156 participants were randomized to combined vascular screening for abdominal aortic aneurysm, PAD, and hypertension or to no screening. Vascular screening was associated with increased pharmacologic therapy (antiplatelet, lipid-lowering, and antihypertensive therapy), reduced in-hospital time for PAD and CAD, and reduced mortality (235). Therefore, the committee recommends screening for asymptomatic PAD using ankle-brachial index in people with diabetes at high risk for PAD, including any of the following: age ≥50 years, diabetes with duration ≥10 years, comorbid microvascular disease, clinical evidence of foot complications, or any end-organ damage from diabetes. Therefore, the committee recommends screening people with diabetes and high risk for PAD, including age ≥50 years, diabetes with duration ≥10 years, microvascular disease, clinical evidence of foot complications, or any end-organ damage from diabetes.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity, as performed in the Action for Health in Diabetes (Look AHEAD) trial, may be considered for improving glucose control, fitness, and some ASCVD risk factors (236). Individuals at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the individual has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class.

Clear cardiovascular benefit exists for ACE inhibitor or ARB therapy in people with diabetes. The Heart Outcomes Prevention Evaluation (HOPE) study randomized 9,297 individuals aged ≥55 years with a history of vascular disease or diabetes plus one other cardiovascular risk factor to either ramipril or placebo. Ramipril significantly reduced cardiovascular and all-cause mortality, MI, and stroke (237). ACE inhibitors or ARB therapy also have well-established long-term benefit in people with diabetes and diabetic kidney disease or hypertension, and these agents are recommended for hypertension management in people with known ASCVD (particularly coronary artery disease) (65,66,238). People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression (239–242). β-Blockers should be used in individuals with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function (243,244).

Glucose-Lowering Therapies and Cardiovascular Outcomes

In 2008, the FDA issued guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment of type 2 diabetes amid concerns of increased cardiovascular risk (245). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular and renal outcomes in people with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease (**Table 10.3*A***, **Table 10.3*B***, and **Table 10.3*C***). An expanded review of the effects of glucose-lowering and other therapies in people with CKD is included in Section 11, "Chronic Kidney Disease and Risk Management."

Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes) study demonstrated noninferiority between a DPP-4 inhibitor, linagliptin, and a sulfonylurea, glimepiride, on cardiovascular outcomes despite lower rates of hypoglycemia in the linagliptin treatment group (246). However, results from other new agents have provided a mix of results.

SGLT2 Inhibitor Trials

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, an SGLT2 inhibitor, versus placebo on cardiovascular outcomes in 7,020 people with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for over 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group, HR in the empagliflozin group 0.86 [95% CI 0.74–0.99]; $P = 0.04$ for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62 [95% CI 0.49–0.77]; $P < 0.001$) (11).

Two large outcomes trials of the SGLT2 inhibitor canagliflozin have been conducted that separately assessed *1*) the cardiovascular effects of treatment in individuals at high risk for major adverse cardiovascular events (12) and *2*) the impact of canagliflozin therapy on cardiorenal outcomes in people with diabetes-related CKD (247). First, the CANVAS Program integrated data from two trials. The CANVAS trial that started in 2009 was partially unblinded prior to completion because of the need to file interim cardiovascular outcomes data for regulatory approval of the drug (248). Thereafter, the postapproval CANVAS-Renal (CANVAS-R) trial was started in 2014. Combining both trials, 10,142 participants with type 2 diabetes were randomized to canagliflozin or placebo and were followed for an average of 3.6 years. The mean age of individuals was 63 years, and 66% had a history of cardiovascular disease. The combined analysis of the two trials found that canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86 [95% CI 0.75–0.97]). The specific estimates for canagliflozin versus placebo on the primary composite cardiovascular outcome were HR 0.88 (95% CI 0.75–1.03) for the CANVAS trial and 0.82 (0.66–1.01) for CANVAS-R, with no heterogeneity found between trials. Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97 [95% CI 1.41–2.75]) (12). Second, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial randomized 4,401 people with type 2 diabetes and chronic diabetes–related kidney disease (UACR >300 mg/g and eGFR 30 to <90 mL/min/1.73 m^2) to canagliflozin 100 mg daily or placebo (247). The primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes. The trial was stopped early due to conclusive evidence of efficacy identified during a prespecified interim analysis with no unexpected safety signals. The risk of the primary composite outcome was 30% lower with canagliflozin treatment than with placebo (HR 0.70 [95% CI 0.59–0.82]). Moreover, it reduced the prespecified end point of end-stage kidney disease alone by 32% (HR 0.68 [95% CI 0.54–0.86]). Canagliflozin was additionally found to have a lower risk of the composite of cardiovascular death, MI, or stroke (HR 0.80 [95% CI 0.67–0.95]) as well as lower risk of hospitalizations for heart failure (HR 0.61 [95% CI 0.47–0.80]) and of the composite of cardiovascular death or hospitalization for heart failure (HR 0.69 [95% CI 0.57–0.83]). In terms of safety, no significant increase in lower-limb amputations, fractures, AKI, or hyperkalemia was noted for canagliflozin relative to placebo in CREDENCE. An increased risk for diabetic ketoacidosis was noted, however, with 2.2 and 0.2 events per 1,000 patient-years noted in the canagliflozin and placebo groups, respectively (HR 10.80 [95% CI 1.39–83.65]) (247).

The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was another randomized, double-blind trial that assessed the effects of dapagliflozin versus placebo on cardiovascular and renal outcomes in 17,160 people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD (249). Study participants had a mean age of 64 years, with ~40% of study participants having established ASCVD at baseline—a characteristic of this trial that differs from other large cardiovascular trials where a majority of participants had established cardiovascular disease. DECLARE-TIMI 58 met the prespecified criteria for noninferiority to placebo with respect to major adverse cardiovascular events but did not show a lower rate of major adverse cardiovascular events when compared with placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93 [95% CI 0.84–1.03]; $P = 0.17$). A lower rate of cardiovascular death or hospitalization for heart failure was noted (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73–0.95]; $P = 0.005$), which reflected a lower rate of hospitalization for heart failure (HR 0.73 [95% CI 0.61–0.88]). No difference was seen in cardiovascular death between groups.

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (250), 4,304 individuals with CKD (UACR 200–5,000 mg/g and eGFR 25–75 mL/min/1.73 m^2), with or without diabetes, were randomized to dapagliflozin 10 mg daily or placebo. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Over a median follow-up period of 2.4 years, a primary outcome event occurred in 9.2% of participants in the dapagliflozin group and 14.5% of those in the placebo group. The risk of the primary composite outcome was significantly lower with dapagliflozin therapy compared with placebo (HR 0.61 [95% CI 0.51–0.72]), as were the risks for a renal composite outcome of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal causes (HR 0.56 [95% CI 0.45–0.68]), and a composite of cardiovascular death or hospitalization for heart failure (HR 0.71 [95% CI 0.55–0.92]). The effects of dapagliflozin therapy were similar in individuals with and without type 2 diabetes.

Results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in

Patients With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF), and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER), which assessed the effects of dapagliflozin and empagliflozin in individuals with established heart failure (14,242,251–253), are described below in GLUCOSE-LOWERING THERAPIES AND HEART FAILURE.

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) (254) was a randomized, double-blind trial that established the effects of ertugliflozin versus placebo on cardiovascular outcomes in 8,246 people with type 2 diabetes and established ASCVD. Participants were assigned to the addition of 5 mg or 15 mg of ertugliflozin or to placebo once daily to background standard care. Study participants had a mean age of 64.4 years and a mean duration of diabetes of 13 years at baseline and were followed for a median of 3.0 years. VERTIS CV met the prespecified criteria for noninferiority of ertugliflozin to placebo with respect to the primary outcome of major adverse cardiovascular events (11.9% in the pooled ertugliflozin group and 11.9% in the placebo group; HR 0.97 [95% CI 0.85–1.11]; $P < 0.001$). Ertugliflozin was not superior to placebo for the key secondary outcomes of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; or the composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. The HR for a secondary outcome of hospitalization for heart failure (ertugliflozin vs. placebo) was 0.70 [95% CI 0.54–0.90], consistent with findings from other SGLT2 inhibitor cardiovascular outcomes trials.

GLP-1 Receptor Agonist Trials

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, versus placebo on cardiovascular outcomes in 9,340 people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease (256). Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) than in the placebo group (14.9%) (HR 0.87 [95% CI 0.78–0.97]; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 [95% CI 0.66–0.93]; $P = 0.007$) (256).

Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (257). Semaglutide is a once-weekly GLP-1 receptor agonist approved by the FDA for the treatment of type 2 diabetes. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) was the initial randomized trial powered to test noninferiority of semaglutide for the purpose of regulatory approval (257). In this study, 3,297 people with type 2 diabetes were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 2 years. The primary outcome (the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 108 individuals (6.6%) in the semaglutide group vs. 146 individuals (8.9%) in the placebo group (HR 0.74 [95% CI 0.58–0.95]; $P < 0.001$). More individuals discontinued treatment in the semaglutide group because of adverse events, mainly gastrointestinal. The cardiovascular effects of the oral formulation of semaglutide compared with placebo have been assessed in Peptide Innovation for Early Diabetes Treatment (PIONEER) 6, a preapproval trial designed to rule out an unacceptable increase in cardiovascular risk (257). In this trial of 3,183 people with type 2 diabetes and high cardiovascular risk followed for a median of 15.9 months, oral semaglutide was noninferior to placebo for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (HR 0.79 [95% CI 0.57–1.11]; $P < 0.001$ for noninferiority) (257). The cardiovascular effects of this formulation of semaglutide will be further tested in a large, longer-term outcomes trial.

The Harmony Outcomes trial randomized 9,463 people with type 2 diabetes and cardiovascular disease to once-weekly subcutaneous albiglutide or matching placebo, in addition to their standard care (258). Over a median duration of 1.6 years, the GLP-1 receptor agonist reduced the risk of cardiovascular death, MI, or stroke to an incidence rate of 4.6 events per 100 person-years in the albiglutide group vs. 5.9 events in the placebo group (HR 0.78, $P = 0.0006$ for superiority) (258). This agent is not currently available for clinical use.

The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial was a randomized, double-blind, placebo-controlled trial that assessed the effect of the once-weekly GLP-1 receptor agonist dulaglutide versus placebo on major adverse cardiovascular events in $\sim$9,990 people with type 2 diabetes at risk for cardiovascular events or with a history of cardiovascular disease (259). Study participants had a mean age of 66 years and a mean duration of diabetes of $\sim$10 years. Approximately 32% of participants had history of atherosclerotic cardiovascular events at baseline. After a median follow-up of 5.4 years, the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes occurred in 12.0% and 13.4% of participants in the dulaglutide and placebo treatment groups, respectively (HR 0.88 [95% CI 0.79–0.99]; $P = 0.026$). These findings equated to incidence rates of 2.4 and 2.7 events per 100 person-years, respectively. The results were consistent across the subgroups of individuals with and without history of CV events. All-cause mortality did not differ between groups ($P = 0.067$).

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in people with type 2 diabetes who had had a recent acute coronary event (261). A total of 6,068 people with type 2 diabetes with a recent hospitalization for MI or unstable angina within the previous 180 days were randomized to receive lixisenatide or placebo in addition to standard care and were followed for a median of $\sim$2.1 years. The primary outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina occurred in 406 individuals (13.4%) in the lixisenatide group vs. 399 (13.2%) in the placebo group (HR 1.2 [95% CI 0.89–1.17]), which demonstrated the noninferiority of lixisenatide to placebo

($P < 0.001$) but did not show superiority ($P = 0.81$).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial also reported results with the once-weekly GLP-1 receptor agonist extended-release exenatide and found that major adverse cardiovascular events were numerically lower with use of extended-release exenatide compared with placebo, although this difference was not statistically significant (261). A total of 14,752 people with type 2 diabetes (of whom 10,782 [73.1%] had previous cardiovascular disease) were randomized to receive extended-release exenatide 2 mg or placebo and followed for a median of 3.2 years. The primary end point of cardiovascular death, MI, or stroke occurred in 839 individuals (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 individuals (12.2%; 4.0 events per 100 person-years) in the placebo group (HR 0.91 [95% CI 0.83–1.00]; $P < 0.001$ for noninferiority), but exenatide was not superior to placebo with respect to the primary end point ($P = 0.06$ for superiority). However, all-cause mortality was lower in the exenatide group (HR 0.86 [95% CI 0.77–0.97]). The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

In summary, there are now numerous large randomized controlled trials reporting statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin, with lesser benefits seen with ertugliflozin) and four FDA-approved GLP-1 receptor agonists (liraglutide, albiglutide [although that agent was removed from the market for business reasons], semaglutide [lower risk of cardiovascular events in a moderate-sized clinical trial but one not powered as a cardiovascular outcomes trial], and dulaglutide). Meta-analyses of the trials reported to date suggest that GLP-1 receptor agonists and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in people with type 2 diabetes and established ASCVD (262,263). SGLT2 inhibitors also reduce risk of heart failure hospitalization and progression of kidney disease in people with established ASCVD, multiple risk factors for ASCVD, or albuminuric kidney disease (264,265). In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a GLP-1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many individuals, use of either an SGLT2 inhibitor or a GLP-1 receptor agonist to reduce cardiovascular risk is appropriate. Emerging data suggest that use of both classes of drugs will provide an additive cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist may be considered to provide the complementary outcomes benefits associated with these classes of medication. Evidence to support such an approach includes findings from AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes), an outcomes trial of people with type 2 diabetes and either cardiovascular or kidney disease plus at least one other risk factor randomized to the investigational GLP-1 receptor agonist efpeglenatide or placebo (266). Randomization was stratified by current or potential use of SGLT2 inhibitor therapy, a class ultimately used by $>$15% of the trial participants. Over a median follow-up of 1.8 years, efpeglenatide therapy reduced the risk of incident major adverse cardiovascular events by 27% and of a composite renal outcome event by 32%. Importantly, the effects of efpeglenatide did not vary by use of SGLT2 inhibitors, suggesting that the beneficial effects of the GLP-1 receptor agonist were independent of those provided by SGLT2 inhibitor therapy (267). Efpeglenatide is currently not approved by the FDA for use in the U.S.

Prevention and Treatment of Heart Failure

Prevention of Symptomatic Heart Failure

ACE Inhibitors/ARBs and β-Blockers. Early primary prevention strategies and treatment of associated risk factors reduce incident, symptomatic heart failure and should include lifestyle intervention with diet, physical activity, weight control, and smoking cessation (268–271). The vast majority of incident heart failure is preceded by hypertension; up to 91% of all new heart failure development in the Framingham cohort occurred in people with a previous diagnosis of hypertension (272). Therefore, management of hypertension constitutes a key goal in people with diabetes and stage A or B heart failure. For example, in the UKPDS trial, intensive blood pressure control in people with type 2 diabetes reduced the risk for heart failure by 56% (273). Similarly, in the SPRINT trial, intensive treatment of hypertension decreased the risk for development of incident heart failure by 36% (274). As discussed in the HYPERTENSION/BLOOD PRESSURE CONTROL section above, use of ACE inhibitors or ARBs is the preferred treatment strategy for management of hypertension in people with diabetes, particularly in the presence of albuminuria or coronary artery disease. People with diabetes and stage B heart failure who remain asymptomatic but have evidence of structural heart disease, including history of MI, acute coronary syndrome, or left ventricular ejection fraction (LVEF) $\leq$40%, should be treated with ACE inhibitors/ARBs plus β-blockers according to current treatment guidelines (210). In the landmark Studies of Left Ventricular Dysfunction (SOLVD) study, in which 15% of people had diabetes, treatment with enalapril reduced incident heart failure in people with asymptomatic left ventricular dysfunction by 20% (275). In the Survival and Ventricular Enlargement (SAVE) study, which enrolled asymptomatic people with reduced LVEF after MI, including 23% people with diabetes, treatment with captopril reduced the development of heart failure by 37% (276). Subsequent retrospective analyses from both trials revealed that concomitant use of β-blockers was associated with decreased risk of progression to symptomatic heart failure (277,278). The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study randomized people with a history of MI and reduced LVEF to treatment with carvedilol (279). Approximately half of the study participants were asymptomatic, and 23% of study participants had a history of diabetes. Treatment with carvedilol reduced mortality by 23%, and there was a 14% risk reduction for heart failure hospitalization. Finally, in the Reversal of Ventricular Remodeling With Toprol-XL

(REVERT) trial, in which 45% of the people enrolled had diabetes, metoprolol improved adverse cardiac remodeling in asymptomatic individuals with an LVEF <40% and mild left ventricular dilatation (280).

SGLT Inhibitors. As reviewed in detail in the following section, SGLT2 inhibitors constitute a key treatment approach to reduce cardiovascular disease and heart failure outcomes in people with diabetes. People with type 2 diabetes and increased cardiovascular risk or established cardiovascular disease should be treated with an SGLT2 inhibitor to prevent the development of incident heart failure. This includes people with type 2 diabetes and asymptomatic stage B heart failure. In the EMPA-REG OUTCOME trial, only 10% of study participants had a prior history of heart failure, and treatment with empagliflozin reduced the relative risk for hospitalization from heart failure by 35% (11). In the CANVAS Program, hospitalization from heart failure was reduced by 33% in people allocated to canagliflozin, and only 14% of individuals enrolled had a prior history of heart failure (12). In the DAPA-HF study, only 10% of study participants had a prior history of heart failure, and dapagliflozin reduced cardiovascular mortality and hospitalization for heart failure by 17%, which was consistent across multiple study subgroups regardless of a prior history of heart failure (249). Finally, in the Effect of Sotagliflozin on Cardiovascular and Renal Events in Participants With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial, randomization to the SGLT1/2 inhibitor sotagliflozin reduced the primary outcome of death from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure in people with type 2 diabetes, CKD, and risk for cardiovascular disease (281). Therefore, SGLT inhibitor treatment is recommended in asymptomatic people with type 2 diabetes at risk or with established cardiovascular disease to prevent incident heart failure and hospitalization from heart failure.

Finerenone. Finerenone is a nonsteroidal MRA and has recently been studied in people with diabetes and diabetic kidney disease, including the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) studies. In FIDELIO-DKD, finerenone was compared with placebo for the primary outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes in people with type 2 diabetes and diabetic kidney disease (282). A prespecified secondary outcome was death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure, which was reduced by 13% in the finerenone group. The incidence of heart failure hospitalization occurred less in the finerenone-treated group, and only 7.7% of study participants had a prior history of heart failure. In the FIGARO-DKD trial, finerenone reduced the primary outcome of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure (HR 0.87 [95% CI 0.76–0.98]; *P* = 0.03) in people with type 2 diabetes and diabetic kidney disease (240). Only 7.8% of all participants had a prior history of heart failure, and the incidence of hospitalization for heart failure was reduced in the finerenone-allocated treatment arm (HR 0.71 [95% CI 0.56–0.90]). Owing to these observations, treatment with finerenone is recommended in people with type 2 diabetes and diabetic kidney disease to reduce the risk of progression from stage A heart failure to symptomatic incident heart failure.

Treatment of Symptomatic Heart Failure

In general, current guideline-directed medical therapy for a history of MI and symptomatic stage C and D heart failure in people with diabetes is similar to that for people without diabetes. At these advanced stages of heart failure, a collaborative approach with a cardiovascular specialist is recommended. The treatment recommendations are detailed in current 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure (210).

Glucose-Lowering Medications and Heart Failure: Discussion of Heart Failure Outcomes

Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (283–285). Therefore, thiazolidinedione use should be avoided in people with symptomatic heart failure. Restrictions to use of metformin in people with medically treated heart failure were removed by the FDA in 2006 (286). Observational studies of people with type 2 diabetes and heart failure suggest that metformin users have better outcomes than individuals treated with other antihyperglycemic agents (287); however, no randomized trial of metformin therapy has been conducted in people with heart failure. Metformin may be used for the management of hyperglycemia in people with stable heart failure as long as kidney function remains within the recommended range for use (288).

Recent studies examining the relationship between DPP-4 inhibitors and heart failure have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that individuals treated with the DPP-4 inhibitor saxagliptin were more likely to be hospitalized for heart failure than those given placebo (3.5% vs. 2.8%, respectively) (289). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (290), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (291), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (292)—did not find a significant increase in risk of heart failure hospitalization with DPP-4 inhibitor use compared with placebo. No increased risk of heart failure hospitalization has been identified in the cardiovascular outcomes trials of the GLP-1 receptor agonists lixisenatide, liraglutide, semaglutide, exenatide once weekly, albiglutide, or dulaglutide compared with placebo (**Table 10.3*B***) (255,256, 259–261).

Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors (11,247,249). In EMPA-REG

OUTCOME, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (11). Although the majority of individuals in the study did not have heart failure at baseline, this benefit was consistent in individuals with and without a history of heart failure (13). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions in hospitalization for heart failure, respectively, with SGLT2 inhibitor use versus placebo (12,249). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure, and 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a diabetic kidney disease population with albuminuria (UACR $>$300–5,000 mg/g) (247). These combined findings from four large outcomes trials of three different SGLT2 inhibitors are highly consistent and clearly indicate robust benefits of SGLT2 inhibitors in the prevention of heart failure hospitalizations. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE trials suggested, but did not prove, that SGLT2 inhibitors would be beneficial in the treatment of people with established heart failure. More recently, the placebo-controlled DAPA-HF trial evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in individuals with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less. Of the 4,744 trial participants, 45% had a history of type 2 diabetes. Over a median of 18.2 months, the group assigned to dapagliflozin treatment had a lower risk of the primary outcome (HR 0.74 [95% CI 0.65–0.85]), lower risk of first worsening heart failure event (HR 0.70 [95% CI 0.59–0.83]), and lower risk of cardiovascular death (HR 0.82 [95% CI 0.69–0.98]) compared with placebo. The effect of dapagliflozin on the primary outcome was consistent regardless of the presence or absence of type 2 diabetes (14).

EMPEROR-Reduced assessed the effects of empagliflozin 10 mg once daily versus placebo on a primary composite outcome of cardiovascular death or hospitalization for worsening heart failure in a population of 3,730 individuals with NYHA class II, III, or IV heart failure and an ejection fraction of 40% or less (253). At baseline, 49.8% of participants had a history of diabetes. Over a median follow-up of 16 months, those in the empagliflozin-treated group had a reduced risk of the primary outcome (HR 0.75 [95% CI 0.65–0.86]; $P < 0.001$) and fewer total hospitalizations for heart failure (HR 0.70 [95% CI 0.58–0.85]; $P < 0.001$). The effect of empagliflozin on the primary outcome was consistent irrespective of diabetes diagnosis at baseline. The risk of a prespecified renal composite outcome (chronic dialysis, renal transplantation, or a sustained reduction in eGFR) was lower in the empagliflozin group than in the placebo group (1.6% in the empagliflozin group vs. 3.1% in the placebo group; HR 0.50 [95% CI 0.32–0.77]).

EMPEROR-Preserved, a randomized double-blinded placebo-controlled trial of 5,988 adults with NYHA functional class I–IV chronic HFpEF (LVEF $>$40%), evaluated the efficacy of empagliflozin 10 mg daily versus placebo on top of standard of care on the primary outcome of composite cardiovascular death or hospitalization for heart failure (242). Approximately 50% of subjects had type 2 diabetes at baseline. Over a median of 26.2 months, there was a 21% reduction (HR 0.79 [95% CI 0.69–0.90]; $P < 0.001$) of the primary outcome. The effects of empagliflozin were consistent in people with or without diabetes (242).

In the DELIVER trial, 6,263 individuals with heart failure and an ejection fraction $>$40% were randomized to receive either dapagliflozin or placebo (252). The primary outcome of a composite of worsening heart failure, defined as hospitalization or urgent visit for heart failure, or cardiovascular death was reduced by 18% in individuals treated with dapagliflozin compared with placebo (HR 0.82 [95% CI 0.73–0.92]; $P < 0.001$). Approximately 44% of individuals randomized to either dapagliflozin or placebo had type 2 diabetes, and results were consistent regardless of the presence of type 2 diabetes.

A large recent meta-analysis (293) of data from EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, DELIVER, and the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial included 21,947 individuals and demonstrated reduced risk for the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, first hospitalization for heart failure, and all-cause mortality. The findings on the studied end points were consistent in both trials of heart failure with mildly reduced or preserved ejection fraction and in all five trials combined. Collectively, these studies indicate that SGLT2 inhibitors reduce the risk for heart failure hospitalization and cardiovascular death in a wide range of people with heart failure.

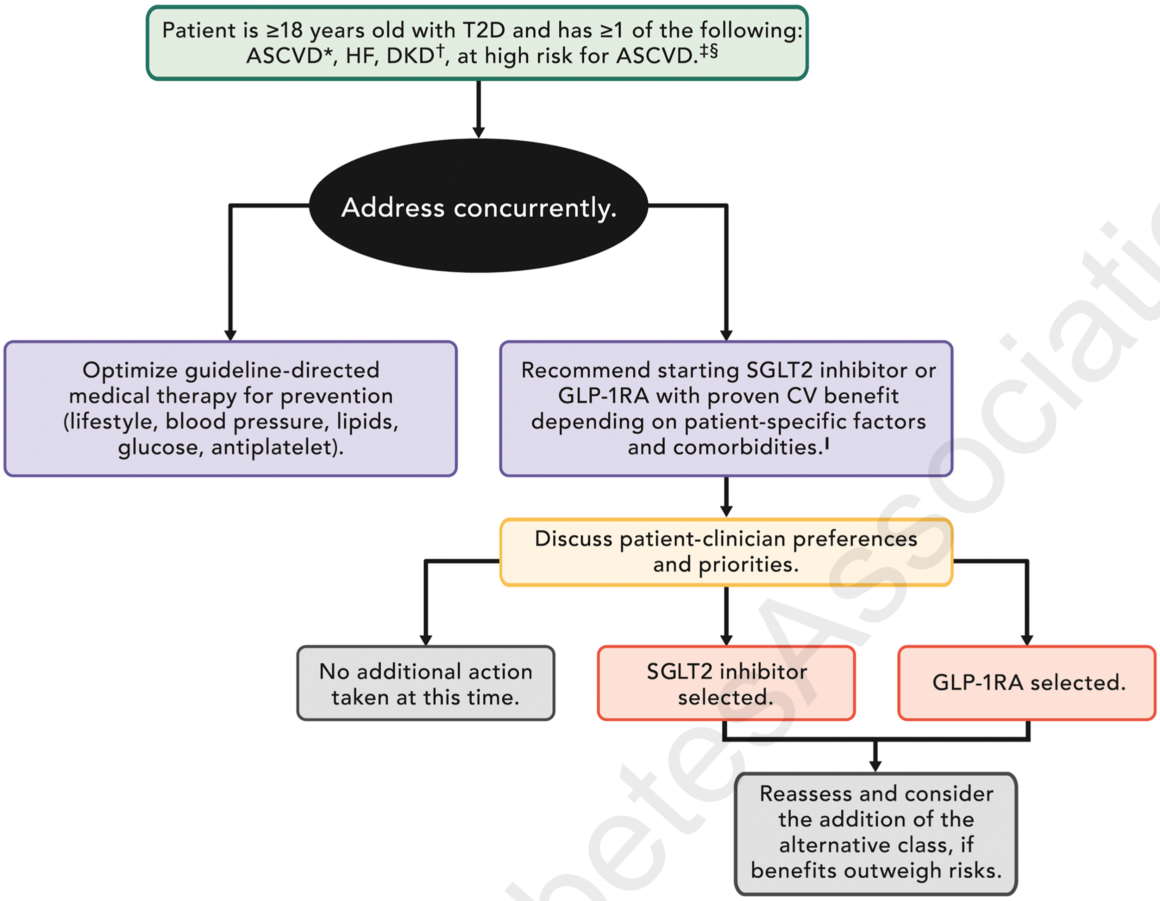
In addition to the hospitalization and mortality benefit in people with heart failure, several recent analyses have addressed whether SGLT2 inhibitor treatment improves clinical stability and functional status in individuals with heart failure. In 3,730 individuals with NYHA class II–IV heart failure with an ejection fraction of $\leq$40%, treatment with empagliflozin reduced the combined risk of death, hospitalization for heart failure, or an emergent/urgent heart failure visit requiring intravenous treatment and reduced the total number of hospitalizations for heart failure requiring intensive care, a vasopressor or positive inotropic drug, or mechanical or surgical intervention (294). In addition, individuals treated with empagliflozin were more likely to experience an improvement in NYHA functional class (294). In people hospitalized for acute de novo or decompensated chronic heart failure, initiation of empagliflozin treatment during hospitalization reduced the primary outcome of a composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (295). Furthermore, PRESERVED-HF, a multicenter study (26 sites in the U.S.), showed that dapagliflozin treatment leads to significant improvement in both symptoms and physical limitation as well as objective measures of exercise function in people with chronic HFpEF, regardless of diabetes status (251). Finally, canagliflozin improved heart failure symptoms assessed using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score, irrespective of LVEF or the presence of diabetes (296). Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure and cardiovascular death. In addition, an SGLT2 inhibitor is recommended in this patient population to improve symptoms, physical limitations, and quality of life. The benefits seen in this patient population likely represent a class effect, and they appear unrelated to glucose lowering, given comparable outcomes in people with heart failure with and without diabetes.

Sotagliflozin

Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, was recently approved by the FDA in the U.S. to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure in people with heart failure or type 2 diabetes, CKD, and other cardiovascular risk factors. This drug is distinct from other SGLT inhibitors, as it lowers glucose via delayed glucose absorption in the gut via inhibition of the cotransporter SGLT1 in addition to increasing urinary glucose excretion; however, it is not currently approved by the FDA for glycemic management of type 1 or type 2 diabetes. Sotagliflozin was evaluated in the SCORED trial (281) and SOLOIST-WHF trial (297). A total of 10,584 people with type 2 diabetes, CKD, and additional cardiovascular risk were enrolled in SCORED and randomized to sotagliflozin 200 mg once daily (uptitrated to 400 mg once daily if tolerated) or placebo. SCORED ended early due to a lack of funding; thus, changes to the prespecified primary end points were made prior to unblinding to accommodate a lower-than-anticipated number of end point events. The primary end point of the trial was the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. After a median of 16 months of follow-up, the rate of primary end point events was reduced with sotagliflozin (5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group [HR 0.74; [95% CI 0.63–0.88]; $P < 0.001$]). Sotagliflozin also reduced the risk of the secondary end point of total number of hospitalizations for heart failure and urgent visits for heart failure (3.5% in the sotagliflozin group and 5.1% in the placebo group [HR 0.67 [95% CI 0.55–0.82]; $P < 0.001$]) but not the secondary end point of deaths from cardiovascular causes. No significant between-group differences were found for the outcome of all-cause mortality or for a composite renal outcome comprising the first occurrence of long-term dialysis, renal transplantation, or a sustained reduction in eGFR. In general, the adverse effects of sotagliflozin were similar to those seen with use of SGLT2 inhibitors, but they also included an increased rate of diarrhea potentially related to the inhibition of SGLT1. In general, the adverse effects of sotagliflozin were similar to those seen with use of SGLT2 inhibitors, but they also included an increased rate of diarrhea potentially related to the inhibition of SGLT1.

In SOLOIST-WHF, 1,222 people with type 2 diabetes who were recently hospitalized for worsening heart failure were randomized to sotagliflozin 200 mg once daily (with uptitration to 400 mg once daily if tolerated) or placebo either before or within 3 days after hospital discharge. Individuals were eligible if hospitalized for signs and symptoms of heart failure (including elevated natriuretic peptide levels) requiring treatment with intravenous diuretic therapy. Exclusion criteria included end-stage heart failure, recent acute coronary syndrome or intervention, or an eGFR $<$30 mL/min/1.73 m^2. Individuals were required to be clinically stable prior to randomization, which was defined as no use of supplemental oxygen, systolic blood pressure $\geq$100 mmHg, and no need for intravenous inotropic or vasodilator therapy other than nitrates. Similar to SCORED, SOLOIST-WHF ended early due to a lack of funding, resulting in a change to the prespecified primary end point prior to unblinding to accommodate a lower-than-anticipated number of end point events. At a median follow-up of 9 months, the rate of primary end point events (the total number of cardiovascular deaths and hospitalizations and urgent visits for heart failure) was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; HR 0.67 [95% CI 0.52–0.85]; $P < 0.001$). No significant between-group differences were found in the rates of cardiovascular death or all-cause mortality. Both diarrhea (6.1% vs. 3.4%) and severe hypoglycemia (1.5% vs. 0.3%) were more common with sotagliflozin than with placebo. The trial was originally also intended to evaluate the effects of SGLT inhibition in people with HFpEF, and ultimately no evidence of heterogeneity of treatment effect by ejection fraction was noted. However, the relatively small percentage of such individuals enrolled (only 21% of participants had ejection fraction $>$50%) and the early termination of the trial limited the ability to determine the effects of sotagliflozin in HFpEF specifically (297).

One concern with expanded use of SGLT inhibition is the infrequent but serious risk of diabetic ketoacidosis, including the atypical presentation of euglycemic ketoacidosis. There are multiple proposed pathways through which SGLT inhibition results in ketosis (increased β-hydroxybutyrate and acetoacetate), such as increased production due to reduction in insulin doses, increases in glucagon levels leading to increased lipolysis and ketone production, and decreased renal clearance of ketones (298,299). Thus, the use of SGLT inhibitors (whether for glycemic control or another indication) increases the susceptibility to diabetic ketoacidosis, particularly when other risk factors or situations occur (including, but not limited to, insulin pump malfunctions, significant reduction in insulin doses, and nutritional intake plans with prolonged periods of fasting or carbohydrate restriction). Although there were low rates of ketoacidosis in the cardiovascular and heart failure outcomes trials evaluating SGLT inhibition, these studies excluded individuals with type 1 diabetes and/or recent history of diabetic ketoacidosis (297,300). To decrease the risk of ketoacidosis when using SGLT inhibition in people with type 1 diabetes, it is recommended that clinicians assess the underlying susceptibility; provide education regarding the risks, symptoms, and prevention strategies; and prescribe home monitoring supplies for β-hydroxybutyrate (299,301). Use of these processes may have contributed to the lower rates of ketoacidosis seen in some of the studies of these agents for adjunctive glycemic management in people with type 1 diabetes (302–304) compared with those that did not include preventative strategies (298,305). Reassessment of susceptibility, education, and provision of monitoring supplies should reoccur throughout the duration of SGLT inhibitor treatment, particularly as preventative strategies and monitoring can minimize, but not eliminate, the risk of ketoacidosis in those who are susceptible (306,307).


Patient is ≥18 years old with T2D and has ≥1 of the following: ASCVD*, HF, DKD†, at high risk for ASCVD.‡§
Address concurrently.
Optimize guideline-directed medical therapy for prevention (lifestyle, blood pressure, lipids, glucose, antiplatelet).
Recommend starting SGLT2 inhibitor or GLP-1RA with proven CV benefit depending on patient-specific factors and comorbidities.ǀ
Discuss patient-clinician preferences and priorities.
No additional action taken at this time.
SGLT2 inhibitor selected.
GLP-1RA selected.
Reassess and consider the addition of the alternative class, if benefits outweigh risks.

[*] ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

[†] DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

[‡] Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

[§] Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

[ǀ] Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

Figure 10.3—Approach to risk reduction with sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. Reprinted with permission from Das et al. (309).

Finerenone in People With Type 2 Diabetes and Chronic Kidney Disease

As discussed in detail in Section 11, “Chronic Kidney Disease and Risk Management,” people with diabetes are at an increased risk for CKD, which increases cardiovascular risk (308). Finerenone, a selective nonsteroidal MRA, has been shown in the FIDELIO-DKD trial to improve CKD outcomes in people with type 2 diabetes with stage 3 or 4 CKD and severe albuminuria (281). In the FIGARO-DKD trial, 7,437 individuals with UACR 30–300 mg/g and eGFR 25–90 mL/min/1.73 m^2 or UACR 300–5,000 and eGFR ≥60 mL/min/1.73 m^2 on maximum dose of renin-angiotensin system blockade were randomized to receive finerenone or placebo (240). The HR of the primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization from heart failure was reduced by 13% in individuals treated with finerenone. A prespecified subgroup analysis from FIGARO-DKD further revealed that in individuals without symptomatic HFrEF, finerenone reduces the risk for new-onset heart failure and improves heart failure outcomes in people with type 2 diabetes and CKD (239). Finally, in the pooled analysis of 13,026 people with type 2 diabetes and CKD from both FIDELIO-DKD and FIGARO-DKD, the HR for the composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure as well as a composite of kidney failure, a sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death were 0.86 and 0.77, respectively (241). These collective studies indicate that finerenone improves cardiovascular and renal outcomes in people with type 2 diabetes. Therefore, in people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, addition of finerenone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.

Clinical Approach

As has been carefully outlined in **Fig. 9.3** in Section 9, "Pharmacologic Approaches to Glycemic Treatment," people with type 2 diabetes with or at high risk for ASCVD, heart failure, or CKD should be treated with a cardioprotective SGLT2 inhibitor and/or GLP-1 receptor agonist as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the plan of care irrespective of the need for additional glucose lowering and irrespective of metformin use. Such an approach has also been described in the ADA-endorsed American College of Cardiology "2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes" (309). **Figure 10.3**, reproduced from that decision pathway, outlines the approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy.

Adoption of these agents should be reasonably straightforward in people with established cardiovascular or kidney disease who are later diagnosed with diabetes, as the cardioprotective agents can be used from the outset of diabetes management. On the other hand, incorporation of SGLT2 inhibitor or GLP-1 receptor agonist therapy in the care of individuals with more long-standing diabetes may be more challenging, particularly if individuals are using an already complex glucose-lowering plan. In such individuals, SGLT2 inhibitor or GLP-1 receptor agonist therapy may need to replace some or all of their existing medications to minimize risks of hypoglycemia and adverse side effects and potentially to minimize medication costs. Close collaboration between primary and specialty care professionals can help to facilitate these transitions in clinical care and, in turn, improve outcomes for high-risk people with type 2 diabetes.

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11. Chronic Kidney Disease and Risk Management: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S219–S230 | https://doi.org/10.2337/dc24-S011

*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

CHRONIC KIDNEY DISEASE

Screening

Recommendations

11.1a At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate [eGFR] should be assessed in people with type 1 diabetes with duration of ≥5 years and in all people with type 2 diabetes regardless of treatment. **B**

11.1b In people with established chronic kidney disease (CKD), urinary albumin (e.g., spot UACR) and eGFR should be monitored 1–4 times per year depending on the stage of the kidney disease (**Fig. 11.1**). **B**

Treatment

Recommendations

11.2 Optimize glucose management to reduce the risk or slow the progression of CKD. **A**

11.3 Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD and reduce cardiovascular risk. **A**

11.4a In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) **B** and is strongly recommended for those with severely increased albuminuria (UACR ≥300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m^2 to prevent the progression of kidney disease and reduce cardiovascular events. **A**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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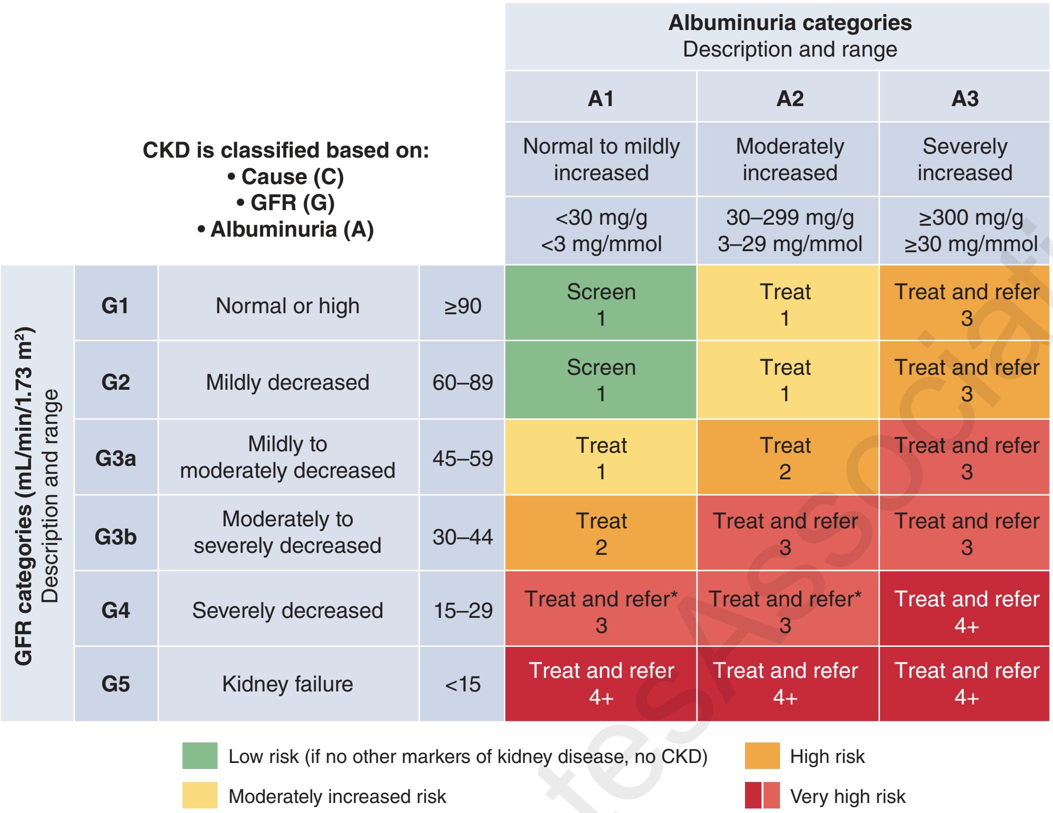

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal or high	≥90	🟩 Screen 1	🟨 Treat 1	🟧 Treat and refer 3
	G2	Mildly decreased	60–89	🟩 Screen 1	🟨 Treat 1	🟧 Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	🟨 Treat 1	🟧 Treat 2	🟥 Treat and refer 3
	G3b	Moderately to severely decreased	30–44	🟧 Treat 2	🟥 Treat and refer 3	🟥 Treat and refer 3
	G4	Severely decreased	15–29	🟥 Treat and refer* 3	🟥 Treat and refer* 3	🟥 Treat and refer 4+
	G5	Kidney failure	<15	🟥 Treat and refer 4+	🟥 Treat and refer 4+	🟥 Treat and refer 4+

🟩 Low risk (if no other markers of kidney disease, no CKD)

🟧 High risk

🟨 Moderately increased risk

🟥 Very high risk

Figure 11.1—Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months, [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as well as the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Reprinted and adapted from de Boer et al. (1).

11.4b Periodically monitor for increased serum creatinine and potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists are used, or for hypokalemia when diuretics are used. **B**

11.4c An ACE inhibitor or an ARB is not recommended for the primary prevention of CKD in people with diabetes who have normal blood pressure, normal UACR (<30 mg/g creatinine), and normal eGFR. **A**

11.4d Do not discontinue renin-angiotensin system blockade for mild to moderate increases in serum creatinine (≤30%) in the absence of signs of extracellular fluid volume depletion. **A**

11.5a For people with type 2 diabetes and CKD, use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine. **A**

11.5b For people with type 2 diabetes and CKD, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. **B**

11.5c For cardiovascular risk reduction in people with type 2 diabetes and CKD, consider use of an SGLT2 inhibitor (if eGFR is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if eGFR is ≥25 mL/min/1.73 m^2). **A**

11.5d As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is ≥25 mL/min/1.73 m^2). Potassium levels should be monitored. **A**

11.6 In people with CKD who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow CKD progression. **C**

11.7 For people with non–dialysis-dependent stage G3 or higher CKD, dietary protein intake should be aimed to a target level of 0.8 g/kg body weight per day. **A** For individuals on dialysis, 1.0–1.2 g/kg/day of dietary protein intake should be considered since protein energy wasting is a major problem in some individuals on dialysis. **B**

11.8 Individuals should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing eGFR and/or if the eGFR is <30 mL/min/1.73 m^2. **A**

11.9 Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **B**

EPIDEMIOLOGY OF DIABETES AND CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1). In this section, the focus is on CKD attributed to diabetes (diabetic kidney disease) in adults, which occurs in 20–40% of people with diabetes (1–4). Diabetic kidney disease typically develops after a diabetes duration of 10 years in type 1 diabetes (the most common presentation is 5–15 years after the diagnosis of type 1 diabetes) but may be present at diagnosis of type 2 diabetes. CKD can progress to end-stage kidney disease (ESKD) requiring dialysis or kidney transplantation and is the leading cause of ESKD in the U.S. (5). In addition, among people with type 1 or type 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (6). For details on the management of diabetic kidney disease in children, please see Section 14, "Children and Adolescents."

ASSESSMENT OF ALBUMINURIA AND ESTIMATED GLOMERULAR FILTRATION RATE

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection (1). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration (7). Thus, semiquantitative or qualitative (dipstick) screening will need to be confirmed by UACR values in an accredited laboratory (8,9). Hence, it is better to simply collect a spot urine sample for albumin-to-creatinine ratio because it will ultimately need to be done.

Normal level of urine albumin excretion is defined as <30 mg/g creatinine, moderately elevated albuminuria is defined as ≥ 30–300 mg/g creatinine, and severely elevated albuminuria is defined as ≥ 300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with kidney and cardiovascular outcomes (6,10,11). Furthermore, because of high biological variability of $>20\%$ between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering an individual to have moderately or severely elevated albuminuria (1,12,13). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (14).

Traditionally, eGFR is calculated from serum creatinine using a validated formula (15). eGFR is routinely reported by laboratories along with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently <60 mL/min/1.73 m^2 and/or an urinary albumin value of >30 mg/g creatinine is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults over age 70 years (1,16). Historically, a correction factor for muscle mass was included in a modified equation for African American people; however, race is a social and not a biologic construct, making it problematic to apply race to clinical algorithms, and the need to advance health equity and social justice is clear. Thus, it was decided that the equation should be altered such that it applies to all. Hence, a committee was convened, resulting in the recommendation for immediate implementation of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation refit without the race variable in all laboratories in the U.S. (17). The CKD-EPI Refit equation is the eGFR formula that is now recommended for everyone (18). Additionally, increased use of cystatin C (another marker of eGFR) is suggested in combination with serum creatinine because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone.

DIAGNOSIS OF DIABETIC KIDNEY DISEASE

Diabetic kidney disease is a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of diabetic kidney disease may be present at diagnosis or without retinopathy in type 2 diabetes. Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (2,3,16,19–21). An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or total proteinuria, the presence of nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease. For individuals with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for people with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (22).

STAGING OF CHRONIC KIDNEY DISEASE

Stage G1 and stage G2 CKD are defined by evidence of high albuminuria with eGFR ≥ 60 mL/min/1.73 m^2, and stages G3–G5 CKD are defined by progressively lower ranges of eGFR (23) (**Fig. 11.1**). At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (6). Therefore, there is an additional subclassification by level of urine albumin (**Fig. 11.1**). Furthermore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex and does not translate directly to treatment decisions (1). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. Quantification of eGFR levels is essential for modifications of medication dosages or restrictions of use (**Fig. 11.1**) (23,24), and the degree of albuminuria should influence the choice of antihypertensive medications (see Section 10, “Cardiovascular Disease and Risk Management”) or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including possible causes other than diabetes) may also affect these decisions (25).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is diagnosed by a sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (26,27). People with diabetes are at higher risk of AKI than those without diabetes (28). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), certain intravenous dyes (e.g., iodinated radiocontrast agents) and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease (29) or high CVD risk with normal kidney function (30–32). It is also noteworthy that the nonsteroidal mineralocorticoid receptor antagonists (MRAs) do not increase the risk of AKI when used to slow kidney disease progression (33). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (34).

Elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (35). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrated that participants randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (36,37). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (37). Accordingly, ACE inhibitors and ARBs should not be discontinued for increases in serum creatinine (<30%) in the absence of volume depletion.

SURVEILLANCE

Both albuminuria and eGFR should be monitored annually to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose medications appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored in individuals treated with diuretics because these medications can cause hypokalemia, which is associated with cardiovascular risk and mortality (38–40). Individuals with eGFR <60 mL/min/1.73 m^2 receiving ACE inhibitors, ARBs, or MRAs should have serum potassium measured periodically. Additionally, people with this lower range of eGFR should have their medication dosing verified, their exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and they should be evaluated for potential CKD complications (**Table 11.1**).

There is a clear need for annual quantitative assessment of urinary albumin excretion. This is especially true after a diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy to maximum tolerated doses, and achievement of blood pressure targets. Early changes in kidney function may be detected by increases in albuminuria before changes in eGFR (41), and this also significantly affects cardiovascular risk. Moreover, an initial reduction of >30% from baseline, subsequently maintained over at least 2 years, is considered a valid surrogate for renal benefit by the Division of Cardiology and Nephrology of the U.S. Food and Drug Administration (FDA) (9). Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in people with type 2 diabetes, reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to maximize reduction in UACR. Data from post hoc analyses demonstrate less benefit on cardiorenal outcomes at half doses of RAS blockade (42). In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (43,44).

The prevalence of CKD complications correlates with eGFR (40). When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 11.1**). Early vaccination against hepatitis B virus is indicated in individuals likely to progress to ESKD (see Section 4, “Comprehensive Medical Evaluation and Assessment of Comorbidities,” for further information on immunization).

Prevention

The only proven primary prevention interventions for CKD in people with diabetes are blood glucose (A1C goal of 7%) and blood pressure control (blood pressure <130/80 mmHg). There is no evidence that renin-angiotensin-aldosterone system inhibitors or any other interventions prevent the development of diabetic kidney disease in the absence of hypertension or albuminuria. Thus, the American Diabetes Association does not recommend routine use of these medications solely for the purpose of prevention of the development of diabetic kidney disease.

Table 11.1—Screening for selected complications of chronic kidney disease

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight, BMI
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron, iron saturation, ferritin testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage G3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage G3 CKD, every 3–5 months for stage G4 CKD, and every 1–3 months for stage G5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

INTERVENTIONS

Nutrition

For people with non–dialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter blood glucose levels, cardiovascular risk measures, or the course of GFR decline (45).

Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk (46,47), and individualization of dietary potassium may be necessary to control serum potassium concentrations (28,38–40). These interventions may be most important for individuals with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For individuals on dialysis, higher levels of dietary protein intake should be considered since malnutrition is a major problem for some individuals on dialysis (48). Recommendations for dietary sodium and potassium intake should be individualized based on comorbid conditions, medication use, blood pressure, and laboratory data.

Glycemic Goals

Intensive lowering of blood glucose with the goal of achieving near-normoglycemia has been shown in large, randomized studies to delay the onset and progression of albuminuria and reduce eGFR in people with type 1 diabetes (49,50) and type 2 diabetes (1,51–56). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that lowering blood glucose itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C goals.

The presence of CKD affects the risks and benefits of intensive lowering of blood glucose and a number of specific glucose-lowering medications. Adverse effects of intensive management of blood glucose levels (hypoglycemia and mortality) were increased among people with kidney disease at baseline (57). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (54,58,59). Therefore, in some people with prevalent CKD and substantial comorbidity, treatment may be less intensive (i.e., A1C goals may be higher) to decrease the risk of hypoglycemia (1,60). A1C levels are also less reliable at advanced CKD stages.

Blood Pressure and Use of ACE Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors and ARBs remain a mainstay of management for people with CKD with albuminuria and for the treatment of hypertension in people with diabetes (with or without diabetic kidney disease). Indeed, all the trials that evaluated the benefits of SGLT2 inhibition or nonsteroidal mineralocorticoid receptor antagonist effects were done in individuals who were being treated with an ACE inhibitor or ARB, in some trials up to maximum tolerated doses.

Hypertension is a strong risk factor for the development and progression of CKD (61). Antihypertensive therapy reduces the risk of albuminuria (62–65), and among people with type 1 or 2 diabetes with established CKD (eGFR <60 mL/min/1.73 m^2 and UACR ≥300 mg/g creatinine), ACE inhibitor or ARB therapy reduces the risk of progression to ESKD (66–75). Moreover, antihypertensive therapy reduces the risk of cardiovascular events (62).

A blood pressure level <130/80 mmHg is recommended to reduce CVD mortality and slow CKD progression among all people with diabetes. Lower blood pressure goals (e.g., <130/80 mmHg) should be considered based on individual anticipated benefits and risks. People with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD; therefore, lower blood pressure goals may be suitable in some cases, especially in individuals with severely elevated albuminuria (≥300 mg/g creatinine).

ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment among people with diabetes, hypertension, eGFR <60 mL/min/1.73 m^2, and UACR ≥300 mg/g creatinine because of their proven benefits for prevention of CKD progression (66,67,69). ACE inhibitors and ARBs are considered to have similar benefits (70,71) and risks. In the setting of lower levels of albuminuria (30–299 mg/g creatinine), ACE inhibitor or ARB therapy at maximum tolerated doses in trials has reduced progression to more advanced albuminuria (≥300 mg/g creatinine), slowed CKD progression, and reduced cardiovascular events but has not reduced progression to ESKD (69,72). While ACE inhibitors or ARBs are often prescribed for moderately increased albuminuria (30–299 mg/g creatinine) without hypertension, outcome trials have not been performed in this setting to determine whether they improve renal outcomes. Moreover, two long-term, double-blind studies demonstrated no renoprotective effect of either ACE inhibitors or ARBs among people with type 1 and type 2 diabetes who were normotensive with or without high albuminuria (formerly microalbuminuria, 30–299 mg/g creatinine) (73,74).

It should be noted that ACE inhibitors and ARBs are commonly not dosed at maximum tolerated doses because of concerns that serum creatinine will rise. As previously noted, not maximizing these therapies for this reason would be considered suboptimal care. Note that in all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the maximum tolerated doses were used—not very low doses that do not provide benefit. Moreover, there are now studies demonstrating outcome benefits on both mortality and slowed CKD progression in people with diabetes who have an eGFR $<$30 mL/min/1.73 m^2 (75). Additionally, when increases in serum creatinine reach 30% without associated hyperkalemia, RAS blockade should be continued (36,76).

In the absence of kidney disease, ACE inhibitors or ARBs are useful to manage blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (77). In a trial of people with type 2 diabetes and normal urinary albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (78). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (73). This was further supported by a similar trial in people with type 2 diabetes (74).

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the medication combination had higher adverse event rates (hyperkalemia and/or AKI) (79,80). Therefore, the combined use of ACE inhibitors and ARBs should be avoided.

Direct Renal Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (31,81–84). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by $>$50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity (84–86). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo, although a definitive resolution as to the renoprotective effects of GLP-1 RAs is yet to be determined (87–91). Renal effects should be considered when selecting agents for glucose lowering (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Selection of Glucose-Lowering Medications for People With Chronic Kidney Disease

For people with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate risks of CKD progression, CVD, and hypoglycemia (92,93). Medication dosing may require modification with eGFR $<$60 mL/min/1.73 m^2 (1). **Figure 11.2** shows the American Diabetes Association and KDIGO consensus recommendation algorithm for medications in people with diabetes and CKD.

The FDA revised its guidance for the use of metformin in CKD in 2016 (94), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of people with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that *1*) metformin is contraindicated in individuals with an eGFR $<$30 mL/min/1.73 m^2, *2*) eGFR should be monitored while taking metformin, *3*) the benefits and risks of continuing treatment should be reassessed when eGFR falls to $<$45 mL/min/1.73 m^2 (95,96), *4*) metformin should not be initiated for individuals with an eGFR $<$45 mL/min/1.73 m^2, and *5*) metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in individuals with eGFR 30–60 mL/min/1.73 m^2.

A number of recent studies have shown cardiovascular protection from SGLT2 inhibitors and GLP-1 RAs as well as renal protection from SGLT2 inhibitors and possibly from GLP-1 RAs. Selection of which glucose-lowering medications to use should be based on the usual criteria of an individual's risks (cardiovascular and renal in addition to glucose control) as well as convenience and cost.

SGLT2 inhibitors are recommended for people with eGFR $\geq$20 mL/min/1.73 m^2 and type 2 diabetes, as they slow CKD progression and reduce heart failure risk independent of glucose management (97). GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression (98–101).

A number of large cardiovascular outcomes trials in people with type 2 diabetes at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (83,87,90,102). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR $>$300 mg/g creatinine, doubling of serum creatinine, ESKD, or death from ESKD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR $\leq$45 mL/min/1.73 m^2 by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESKD, or death from ESKD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESKD, or death from ESKD) by 22%; and

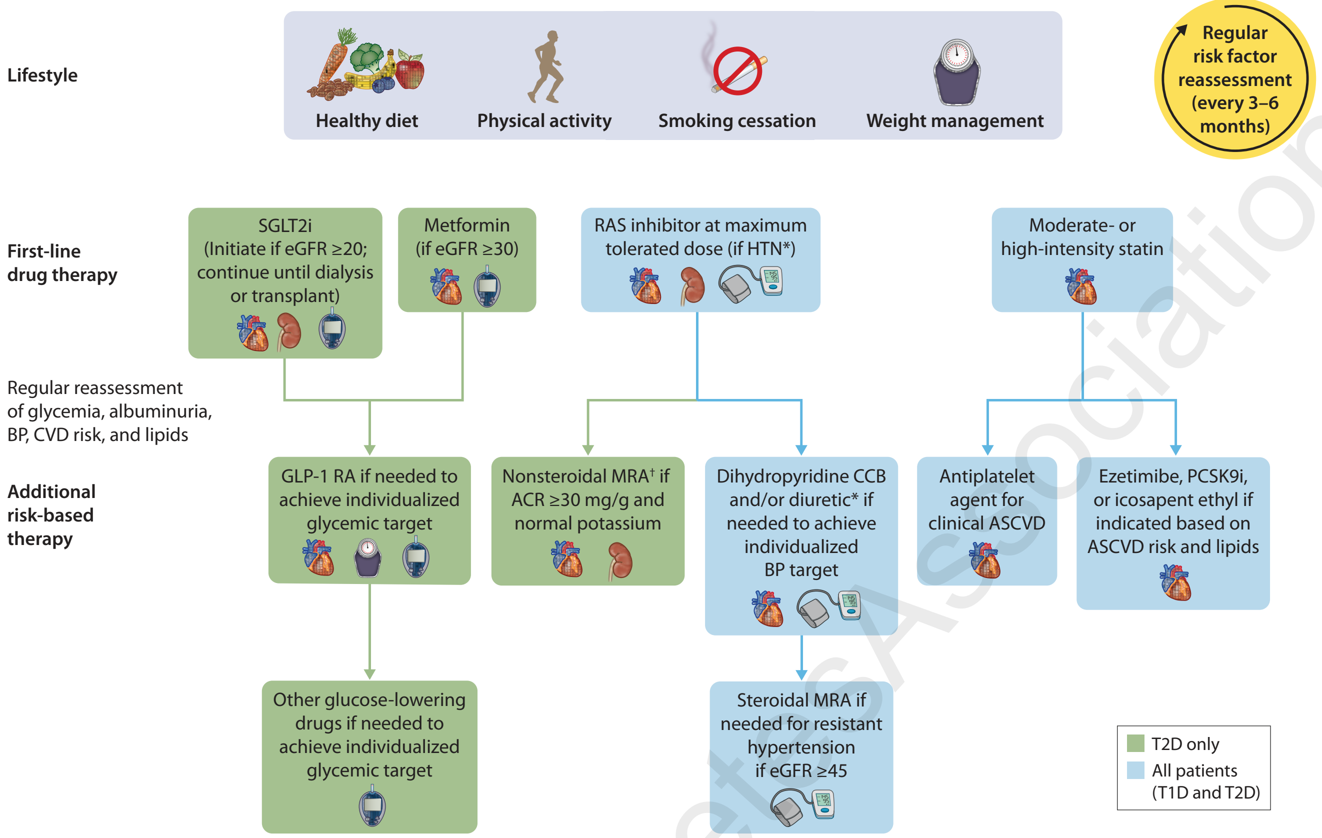
Lifestyle
Healthy diet
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
First-line drug therapy
SGLT2i (Initiate if eGFR ≥20; continue until dialysis or transplant)
Metformin (if eGFR ≥30)
RAS inhibitor at maximum tolerated dose (if HTN*)
Moderate- or high-intensity statin
Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids
Additional risk-based therapy
GLP-1 RA if needed to achieve individualized glycemic target
Nonsteroidal MRA† if ACR ≥30 mg/g and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids
Other glucose-lowering drugs if needed to achieve individualized glycemic target
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
T2D only
All patients (T1D and T2D)

Figure 11.2—Holistic approach for improving outcomes in people with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. Reprinted from de Boer et al. (1).

semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g creatinine, doubling of serum creatinine, or ESKD) by 36% (each $P < 0.01$). These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of renal effects as secondary outcomes.

Three large clinical trials of SGLT2 inhibitors have focused on people with CKD and assessment of primary renal outcomes. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR ≥300–5,000 mg/g creatinine, and eGFR range 30–90 mL/min/1.73 m^2 (mean eGFR 56 mL/min/1.73 m^2 with a mean albuminuria level of >900 mg/day), had a primary composite end point of ESKD, doubling of serum creatinine, or renal or cardiovascular death (29,103). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESKD over control (29). Additionally, the development of the primary end point, which included dialysis for ≥30 days, kidney transplantation or eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for ≥30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the participants (29). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (29,101, 104).

A second trial in advanced diabetic kidney disease was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study (105). This trial examined a cohort similar to that in CREDENCE except 67.5% of the participants had type 2 diabetes and CKD (the other one-third had CKD without type 2 diabetes), and the end points were slightly different. The primary outcome was time to the first occurrence of any of the components of the composite, including ≥50% sustained decline in eGFR or reaching ESKD or cardiovascular death, or renal death. Secondary outcome measures included time to the first occurrence of any of the components of the composite kidney outcome (≥50% sustained decline in eGFR or reaching ESKD or renal death), time to the first occurrence of either of the components of the cardiovascular composite (cardiovascular death or hospitalization for heart failure), and time to death from any cause. The trial had 4,304 participants with a mean eGFR at baseline of 43.1 ± 12.4 mL/min/1.73 m^2 (range 25–75 mL/min/1.73 m^2) and a median UACR of 949 mg/g (range 200–5,000 mg/g). There was a significant benefit by dapagliflozin for the primary end point (hazard ratio [HR] 0.61 [95% CI 0.51–0.72]; $P < 0.001$) (105). The HR for the kidney composite of a sustained decline in eGFR of ≥50%, ESKD, or death from renal causes was 0.56 (95% CI 0.45–0.68; $P < 0.001$). The HR for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI 0.55–0.92; $P = 0.009$). Finally, all-cause mortality was decreased in the dapagliflozin group compared with the placebo group ($P < 0.004$).

The most recently published clinical trial was EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) (106). This study enrolled participants with kidney disease with an eGFR of at least 20 but less than 45 mL/min/1.73 m^2 or who had an eGFR of at least 45 but less than 90 mL/min/1.73 m^2 with a UACR of at least 200 mg/g creatinine. Approximately one-half of the 6,609 participants had diabetes. The empagliflozin-treated participants had lower risk of progression of kidney disease and lower risk of death from cardiovascular causes (HR 0.72 [95% CI 0.64–0.82]; $P < 0.001$).

With respect to cardiovascular outcomes, SGLT2 inhibitors have demonstrated reduced risk of heart failure hospitalizations and some also demonstrated cardiovascular risk reduction. GLP-1 RAs have clearly demonstrated cardiovascular benefits. (See Section 10, "Cardiovascular Disease and Risk Management," for further detailed discussion.)

Of note, while the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits were still seen at eGFR levels as low as 20 mL/min/1.73 m^2 even with no significant change in glucose (29,31,49,60,90,102,105–107). Most participants with CKD in these trials also had diagnosed atherosclerotic cardiovascular disease (ASCVD) at baseline, although ∼28% of CANVAS participants with CKD did not have diagnosed ASCVD (32).

Based on evidence from the CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials, as well as secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardiovascular and renal events are reduced with SGLT2 inhibitor use in individuals with an eGFR of 20 mL/min/1.73 m^2, independent of glucose-lowering effects (101,104).

While there is clear cardiovascular risk reduction associated with GLP-1 RA use in people with type 2 diabetes and CKD, the possibility for benefit on renal outcomes will come with the results of the ongoing FLOW (A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide (108). As noted above, published data address a limited group of people with CKD, mostly with coexisting ASCVD. Renal events, however, have been examined as both primary and secondary outcomes in large published trials. Adverse event profiles of these agents also must be considered. Please refer to **Table 9.2** for medication-specific factors, including adverse event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in people with CKD are ongoing and will be reported in the next few years.

For people with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors are recommended for individuals at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (**Fig. 9.3**). For people with type 2 diabetes and CKD, use of an SGLT2 inhibitor in individuals with eGFR ≥20 mL/min/1.73 m^2 and UACR ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. The reason for the limit of eGFR is as follows. The major clinical trials for SGLT2 inhibitors that showed benefit for people with diabetic kidney disease are CREDENCE, DAPA-CKD, and EMPA-KIDNEY. CREDENCE enrollment criteria included eGFR >30 mL/min/1.73 m^2 and UACR >300 mg/g (29,101). DAPA-CKD enrolled individuals with eGFR >25 mL/min/1.73 m^2 and UACR >200 mg/g. Subgroup analyses from DAPA-CKD (109) and analyses from the EMPEROR heart failure trials suggest that SGLT2 inhibitors are safe and effective at eGFR levels of >20 mL/min/1.73 m^2. The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) enrolled 5,998 participants (110), and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) enrolled 3,730 participants (111); enrollment criteria included eGFR >60 mL/min/1.73 m^2, but efficacy was seen at eGFR >20 mL/min/1.73 m^2 in people with heart failure. Most recently, the EMPA-KIDNEY trial showed efficacy in participants with eGFR as low as 20 mL/min/1.73 m^2 (106). Hence, the new recommendation is to use SGLT2 inhibitors in individuals with eGFR as low as 20 mL/min/1.73 m^2. In addition, the DECLARE-TIMI 58 trial suggested effectiveness in participants with normal urinary albumin levels (112). In sum, for people with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in people with an eGFR ≥20 mL/min/1.73 m^2.

Of note, GLP-1 RAs may also be used at low eGFR for cardiovascular protection but may require dose adjustment (113).

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

MRAs historically have not been well studied in diabetic kidney disease because of the risk of hyperkalemia (114,115). However, data that do exist suggest sustained benefit on albuminuria reduction. There are two different classes of MRAs, steroidal and nonsteroidal, with one group not extrapolatable to the other (116). Late in 2020, the results of the first of two trials, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, which examined the renal effects of finerenone, demonstrated a significant reduction in diabetic kidney disease progression and cardiovascular events in people with advanced diabetic kidney disease (33,117). This trial had a primary end point of time to first occurrence of the composite end point of onset of kidney failure, a sustained decrease of eGFR >40% from baseline over at least 4 weeks, or renal death. A prespecified secondary outcome was time to first occurrence of the composite end point of cardiovascular death or nonfatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure). Other secondary outcomes included all-cause mortality, time to all-cause hospitalizations, and change in UACR from baseline to month 4, and time to first occurrence of the following composite end point: onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death.

The double-blind, placebo-controlled trial randomized 5,734 people with CKD and type 2 diabetes to receive finerenone, a nonsteroidal MRA, or placebo. Eligible participants had a UACR of 30 to <300 mg/g, an eGFR of 25 to <60 mL/min/1.73 m^2, and diabetic retinopathy, or a UACR of 300–5,000 mg/g and an eGFR of 25 to <75 mL/min/1.73 m^2. The potassium level had to be ≤4.8 mmol/L. The mean age of participants was 65.6 years, and 30% were female. The mean eGFR was 44.3 mL/min/1.73 m^2, and the mean albuminuria was 852 mg/g (interquartile range 446–1,634 mg/g). The primary end point was reduced with finerenone compared with placebo (HR 0.82 [95% CI 0.73–0.93]; *P* = 0.001), as was the key secondary composite of cardiovascular outcomes (HR 0.86 [95% CI 0.75–0.99]; *P* = 0.03). Hyperkalemia resulted in 2.3% discontinuation in the study group compared with 0.9% in the placebo group. However, the study was completed, and there were no deaths related to hyperkalemia. Of note, 4.5% of the total group were being treated with SGLT2 inhibitors.

The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial assessed the safety and efficacy of finerenone in reducing cardiovascular events among people with type 2 diabetes and CKD with elevated UACR (30 to <300 mg/g creatinine) and eGFR 25–90 mL/min/1.73 m^2 (118). The potassium level had to be ≤4.8 mmol/L. The study randomized eligible subjects to either finerenone (*n* = 3,686) or placebo (*n* = 3,666). Participants with an eGFR of 25–60 mL/min/1.73 m^2 at the screening visit received an initial dose at baseline of 10 mg once daily, and if eGFR at screening was ≥60 mL/min/1.73 m^2, the initial dose was 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium level was ≤4.8 mmol/L and eGFR was stable. The mean age of participants was 64.1 years (31% were female), and the median follow-up duration was 3.4 years. The median A1C was 7.7%, the mean systolic blood pressure was 136 mmHg, and the mean GFR was 67.8 mL/min/1.73 m^2. People with heart failure with a reduced ejection fraction and uncontrolled hypertension were excluded.

The primary composite outcome was cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. The finerenone group showed a 13% reduction in the primary end point compared with the placebo group (12.4% vs. 14.2%; HR 0.87 [95% CI 0.76–0.98]; *P* = 0.03). This benefit was primarily driven by a reduction in heart failure hospitalizations: 3.2% vs. 4.4% in the placebo group (HR 0.71 [95% CI 0.56–0.90]).

Of the secondary outcomes, the most noteworthy was a 36% reduction in ESKD: 0.9% vs. 1.3% in the placebo group (HR 0.64 [95% CI 0.41–0.995]). There was a higher incidence of hyperkalemia in the finerenone group, 10.8% vs. 5.3%, although only 1.2% of the 3,686 individuals on finerenone stopped the study due to hyperkalemia.

The FIDELITY prespecified pooled efficacy and safety analysis incorporated individuals from both the FIGARO-DKD and FIDELIO-DKD trials (*N* = 13,171) to allow for evaluation across the spectrum of severity of CKD, since the populations were different (with a slight overlap) and the study designs were similar (119). The analysis showed a 14% reduction in composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure for finerenone vs. placebo (12.7% vs. 14.4%; HR 0.86 [95% CI 0.78–0.95]; *P* = 0.0018).

It also demonstrated a 23% reduction in the composite kidney outcome, consisting of sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death, for finerenone vs. placebo (5.5% vs. 7.1%; HR 0.77 [95% CI 0.67–0.88]; *P* = 0.0002).

The pooled FIDELITY trial analysis confirms and strengthens the positive cardiovascular and renal outcomes with finerenone across the spectrum of CKD, irrespective of baseline ASCVD history (with the exclusion of those with heart failure with reduced ejection fraction).

REFERRAL TO A NEPHROLOGIST

Health care professionals should consider referral to a nephrologist if the individual with diabetes has continuously rising UACR levels and/or continuously declining eGFR, if there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria in spite of good blood pressure management, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR <30 mL/min/1.73 m^2) requiring discussion of renal replacement therapy for ESKD (1). The threshold for referral may vary depending on the frequency with which a health care professional encounters people with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (120).

However, other specialists and health care professionals should also educate people with diabetes about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

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12. Retinopathy, Neuropathy, and Foot Care: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

DIABETIC RETINOPATHY

Recommendations

12.1 Implement strategies to help people with diabetes reach glycemic goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

12.2 Implement strategies to help people with diabetes reach blood pressure and lipid goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific neurovascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control (1). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other eye disorders occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (2,3), nephropathy (4), hypertension (5), and dyslipidemia (6). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy, reduce the need for future ocular surgical procedures, and potentially improve self-reported visual function (2,7–10). A meta-analysis of data from cardiovascular outcomes studies showed no association between glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment and retinopathy per se, except through the association between retinopathy and average A1C reduction at the 3-month and 1-year follow-up. Long-term

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**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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impact of improved glycemic control on retinopathy was not studied in these trials. However, GLP-1 RAs including liraglutide, semaglutide, and dulaglutide have been shown to be associated with an increased risk of rapidly worsening diabetic retinopathy in randomized trials. Further data from clinical studies with longer follow-up purposefully designed for diabetic retinopathy risk assessment, particularly including individuals with established diabetic retinopathy, are warranted. Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy (11).

Screening

Recommendations

12.3 Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**

12.4 People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**

12.5 If there is no evidence of retinopathy from one or more annual eye exams and glycemic indicators are within the goal range, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**

12.6 Programs that use retinal photography with remote reading or the use of U.S. Food and Drug Administration–approved artificial intelligence algorithms to improve access to diabetic retinopathy screening are appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

12.7 Counsel individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant on the risk of development and/or progression of diabetic retinopathy. **B**

12.8 Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy and in the first trimester and should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

The preventive effects of therapy and the fact that individuals with any level of diabetic retinopathy or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy. Prompt diagnosis allows triage of people with diabetes and timely intervention that may prevent vision loss in individuals who are asymptomatic despite advanced diabetic eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (12) (see Section 14, “Children and Adolescents”). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for individuals with type 1 or type 2 diabetes are generally repeated annually for individuals with minimal to no retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-controlled type 2 diabetes, there was little risk of development of significant retinopathy within a 3-year interval after a normal examination (13), and less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in individuals without diabetic retinopathy (14). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as uncontrolled hyperglycemia, advanced baseline retinopathy, or diabetic macular edema are present.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (15–17). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (15,18,19). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for dilated comprehensive eye exams, which should be performed at least initially and at yearly intervals thereafter or more frequently as recommended by an eye care professional. Artificial intelligence systems that detect more than mild diabetic retinopathy and diabetic macular edema, authorized for use by the U.S. Food and Drug Administration (FDA), represent an alternative to traditional screening approaches (20). There are now three FDA-approved artificial intelligence algorithms for diabetic retinopathy screening and examination. These services are now covered by most insurances. There are published prospective multicenter clinical trials on the diagnostic accuracy for each (21–23). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, people with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (14).

Type 2 Diabetes

People with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Individuals who develop gestational diabetes mellitus do not require eye examinations during pregnancy since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (24). However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy. In a systematic review and meta-analysis of 18 observational studies of pregnant individuals with preexisting type 1 or type 2 diabetes, the prevalence of any diabetic retinopathy and proliferative diabetic retinopathy (PDR) in early pregnancy was 52.3% and 6.1%, respectively. The pooled progression rate per 100 pregnancies for new diabetic retinopathy development was 15.0 (95% CI 9.9–20.8), worsened nonproliferative diabetic retinopathy was 31.0 (95% CI 23.2–39.2), pooled sight-threatening progression rate from nonproliferative diabetic retinopathy to PDR was 6.3 (95% CI 3.3–10.0), and worsened PDR was 37.0 (95% CI 21.2–54.0), demonstrating that close follow-up should be maintained during pregnancy to prevent vision loss (25). In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (26).

A systematic review and meta-analysis and a controlled prospective study demonstrate that pregnancy in individuals with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic management is poor or retinopathy severity is advanced at the time of conception (25,26). Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved diabetic macular edema (26). The use of anti–vascular endothelial growth factor (anti-VEGF) injections in pregnant individuals may be justified only if the potential benefit outweighs the potential risk to the fetus and only if clearly indicated. Current anti-VEGF medications have been assigned to pregnancy category C by the FDA (animal studies have revealed evidence of embryo–fetal toxicity, but there are no controlled data in human pregnancy), and caution should be used in pregnant individuals with diabetes because of theoretical risks to the vasculature of the developing fetus.

Treatment

Recommendations

12.9 Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy [PDR]), or any PDR to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**

12.10 Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk PDR and, in some cases, severe nonproliferative diabetic retinopathy. **A**

12.11 Intravitreous injections of anti–vascular endothelial growth factor (anti-VEGF) are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with PDR and also reduce the risk of vision loss in these individuals. **A**

12.12 Intravitreous injections of anti-VEGF are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-VEGF therapy or eyes that are not candidates for this first-line approach. **A**

12.14 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in individuals with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in individuals with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (27) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). Later, the ETDRS verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset individuals with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR (28). Panretinal laser photocoagulation is still commonly used to manage complications of diabetic retinopathy that involve retinal neovascularization and its complications. A more gentle, macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (28), but this is now largely considered to be second-line treatment for diabetic macular edema.

Anti–Vascular Endothelial Growth Factor Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (29,30). In addition, it was observed that individuals treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema (29). However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that individuals were required to have a greater number of visits and received a greater number of treatments than is typically required for management with panretinal laser, which may not be optimal for some individuals. The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and diabetic macular edema but has not been shown to improve visual outcomes over 2 years of therapy and therefore is not routinely recommended for this indication (31).

While the ETDRS (28) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide a more effective treatment plan for center-involved diabetic macular edema than monotherapy with laser (32,33). Most individuals require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from central-involved diabetic macular edema. There are currently five anti-VEGF agents used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, aflibercept, brolucizumab and faricimab (1)—and a comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from diabetic macular edema (34). For eyes that have good vision (20/25 or better) despite diabetic macular edema, close monitoring with initiation of anti-VEGF therapy if vision worsens provides similar 2-year vision outcomes compared with immediate initiation of anti-VEGF therapy (35).

Eyes that have persistent diabetic macular edema despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids. Both of these therapies are also reasonable first-line approaches for individuals who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although strict goals (systolic blood pressure <120 mmHg) do not impart additional benefit (8). In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (36,37).

Visual Rehabilitation

Recommendations

12.15 People who experience vision loss from diabetes should be counseled on the availability and scope of vision rehabilitation care and provided, or referred for, a comprehensive evaluation of their visual impairment by a practitioner experienced in vision rehabilitation. **E**

12.16 People with vision loss from diabetes should receive educational materials and resources for eye care support in addition to self-management education (e.g., glycemic management and hypoglycemia awareness). **E**

In the U.S., ~12% of adults with diabetes have some level of vision impairment (38). They may have difficulty controlling their diabetes and performing many other activities of daily living, which can lead to depression, anxiety, social isolation, and difficulties at home, workplace, school, or workplace (39).

People with diabetes are at increased risk of chronic vision loss, subsequent functional decline, and resulting disability. Vision impairment has physical, psychological, behavioral, and social consequences that affect people with diabetes, their families, friends, and caregivers. Health care professionals and stakeholders may not be aware of the overall impact of vision loss on an individual's health and well-being. People with diabetes-related vision loss should be evaluated to determine their potential to benefit from comprehensive vision restoration. Vision rehabilitation can help people with vision loss achieve maximum function, independence, and quality of life.

NEUROPATHY

Screening

Recommendations

12.17 All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**

12.18 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

12.19 Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in people with diabetes is important. Points to be aware of include the following:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in people with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers (DFUs) and amputations.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment to reverse the underlying nerve damage is currently not available. Glycemic management can effectively prevent diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) in type 1 diabetes (40,41) and may modestly slow their progression in type 2 diabetes (42), but it does not reverse neuronal loss. Treatments of other modifiable risk factors (including lipids and blood pressure) can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes (43–45). Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (46) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Individuals with a type 1 diabetes duration ≥5 years and all individuals with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests (46). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensory polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation.
2. Large-fiber function: lower-extremity reflexes, vibration perception, and 10-g monofilament.
3. Protective sensation: 10-g monofilament.

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical or the diagnosis is unclear.

In all people with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (47). See the American Diabetes Association position statement "Diabetic Neuropathy" for more details (46).

Diabetic Autonomic Neuropathy

Individuals who have had type 1 diabetes for ≥5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy (46). The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating. Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function. Further testing can be considered if symptoms are present and will depend on the end organ involved but might include cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, or endoscopy/colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to hypoglycemia unawareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy. Cardiovascular autonomic neuropathy (CAN) is associated with mortality independently of other cardiovascular risk factors (48,49). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia ($>$100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by $>$20 mmHg or $>$10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies. Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract, with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic management or with upper gastrointestinal symptoms without another identified cause. Exclusion of reversible/iatrogenic causes such as medications or organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is an approved alternative.

Genitourinary Disturbances. Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (46). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (50). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

12.20 Optimize glucose management to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of neuropathy in people with type 2 diabetes. **C** Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic neuropathy. **B**

12.21 Assess and treat pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy to improve quality of life. **E**

12.22 Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A** Refer to neurologist or pain specialist when adequate pain management is not achieved within the scope of practice of the treating clinician. **E**

Glycemic Management

Near-normal glycemic management, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in people with type 1 diabetes (51–54). Although the evidence for the benefit of near-normal glycemic management is not as strong that for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (42,55). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (56). Additionally, recent evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed clear benefit of intensive glucose and blood pressure management on the prevention of CAN in type 2 diabetes (57).

Lipid Management

Dyslipidemia is a key factor in the development of neuropathy in people with type 2 diabetes and may contribute to neuropathy risk in people with type 1 diabetes (58,59). Although the evidence for a relationship between lipids and neuropathy development has become increasingly clear in type 2 diabetes, the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and bariatric surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fenofibrates) does not appear to be effective in treating or preventing DPN development (60).

Blood Pressure Management

There are multiple reasons for blood pressure management in people with diabetes, but neuropathy progression (especially in type 2 diabetes) has now been added to this list. Although data from many studies have supported the role of hypertension in risk of neuropathy development, a recent meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk of DPN development with an odds ratio of 1.58 (61). In the ACCORD trial, intensive blood pressure intervention decreased CAN risk by 25% (57).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (62). No compelling evidence exists in support of glycemic or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (63). A recent guideline by the American Academy of Neurology recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN (64).

A number of pharmacologic therapies exist for treatment of pain in diabetes. The American Academy of Neurology update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, and tricyclic antidepressants (TCAs) could all be considered in the treatment of pain in DPN (64). These American Academy of Neurology recommendations offer a supplement to a recent American Diabetes Association pain monograph (65). A recent head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN (66). The trial also supported the role of combination therapy over monotherapy for the treatment of pain in DPN.

Gabapentinoids. Gabapentinoids include several calcium channel $\alpha 2$-δ subunit ligands. Eight high-quality studies and seven medium-quality studies support the role of pregabalin in treatment of pain in DPN. One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN. Two medium-quality studies suggest that mirogabalin has a small effect on pain in DPN (64). Adverse effects may be more severe in older individuals (67) and may be attenuated by lower starting doses and more gradual titration.

SNRIs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs. Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN. A high-quality study supports the role of venlafaxine in the treatment of pain in DPN. Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN (64). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tapentadol and Tramadol. Tapentadol and tramadol are centrally acting opioid analgesics that exert their analgesic effects through both μ-opioid receptor agonism and norepinephrine and serotonin reuptake inhibition. SNRI/opioid agents are probably effective in the treatment of pain in DPN. However, the use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic Antidepressants. TCAs have been studied for treatment of pain, and most of the relevant data were acquired from trials of amitriptyline and include two high-quality studies and two medium-quality studies supporting the treatment of pain in DPN (64,66). Anticholinergic side effects may be dose limiting and restrict use in individuals $\geq$65 years of age.

Sodium Channel Blockers. Sodium channel blockers include lamotrigine, lacosamide, carbamazepine, oxcarbazepine, and valproic acid. Five medium-quality studies support the role of sodium channel blockers in treating pain in DPN (64).

Capsaicin. Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported. One medium-quality study of 0.075% capsaicin cream has been reported. In individulas with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Lidocaine 5% Plaster/Patch. Lidocaine patches have limited data supporting their use in DPN and are not effective in more widespread distribution of pain (although they may be of use in individuals with nocturnal neuropathic foot pain). Lidocaine patches cannot be used for more than 12 h in a 24-h period (68).

α-Lipoic Acid. α-Lipoic acid, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (64, 65).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most individuals require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures. Additionally, supine blood pressure tends to be much higher in these individuals, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β-blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if an individual is unable to tolerate preferred agents (69–71). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. A low-fiber, low-fat eating plan provided in small frequent meals with a greater proportion of liquid calories may be useful (72–74). In addition, foods with small particle size may improve key symptoms (75). Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, TCAs, GLP-1 RAs, and pramlintide, may also improve intestinal motility (72,76). However, the risk of removal of GLP-1 RAs should be balanced against their potential benefits. In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA. It should be reserved for severe cases that are unresponsive to other therapies (76). Other treatment options include domperidone (available outside the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (77,78). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although there are very limited data in DPN and the results do not support gastric stimulation as an effective therapy in diabetic gastroparesis (79).

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve a person's quality of life.

FOOT CARE

Recommendations

12.23 Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **A**

12.24 The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, or vibration), and vascular assessment, including pulses in the legs and feet. **B**

12.25 Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **A**

12.26 Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**

12.27 Initial screening for peripheral arterial disease (PAD) should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index with toe pressures and for further vascular assessment as appropriate. **B**

12.28 An interprofessional approach facilitated by a podiatrist in conjunction with other appropriate team members is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with PAD). **B**

12.29 Refer individuals who smoke and have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or PAD to foot care specialists for ongoing preventive care and lifelong surveillance. **B**

12.30 Provide general preventive foot self-care education to all people with diabetes, including those with loss of protective sensation, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. **B**

12.31 The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with loss of protective sensation, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

12.32 For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy. **A**

Foot ulcerations and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, peripheral arterial disease (PAD), and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet, preulcerative lesions, and prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes.

Early recognition requires an understanding of those factors that put people with diabetes at increased risk for ulcerations and amputations. Factors that are associated with the at-risk foot include the following:

- Poor glycemic management
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammertoes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy (particularly individuals on dialysis or posttransplant)

Identifying the at-risk foot begins with a detailed history documenting diabetes management, smoking history, exercise tolerance, history of claudication or rest pain, and prior ulcerations or amputations. A thorough examination of the feet should be performed annually in all people with diabetes and more frequently in at-risk individuals (80). The examination should include assessment of skin integrity, assessment for LOPS using the 10-g monofilament along with at least one other neurological assessment tool, pulse examination of the dorsalis pedis and posterior tibial arteries, and assessment for foot deformities such as bunions, hammertoes, and prominent metatarsals, which increase plantar foot pressures and increase risk for ulcerations. At-risk individuals should be assessed at each visit and should be referred to foot care specialists for ongoing preventive care and surveillance. The physical examination can stratify people with diabetes into different categories and determine the frequency of these visits (81) (**Table 12.1**).

Evaluation for Loss of Protective Sensation

The presence of peripheral sensory neuropathy is the single most common component cause for foot ulceration. In a multicenter trial, peripheral neuropathy was found to be a component cause in 78% of people with diabetes with ulcerations and that the triad of peripheral sensory neuropathy, minor trauma, and foot deformity was present in >63% of participants (82). All people with diabetes should undergo a comprehensive foot examination at least annually, or more frequently for those in higher-risk categories (80,81).

LOPS is vital to risk assessment. One of the most useful tests to determine LOPS is the 10-g monofilament test. Studies have shown that clinical examination and the 10-g monofilament test are the two most sensitive tests in identifying the foot at risk for ulceration (83). The monofilament test should be performed with at least one other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device). Absent monofilament sensation and one other abnormal test confirms the presence of LOPS. Further neurological testing, such as nerve conduction, electromyography, nerve biopsy, or intraepidermal nerve fiber density biopsies, are rarely indicated for the diagnosis of peripheral sensory neuropathy (46).

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency. Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time (80,84). Any individual exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings. While ankle-brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people with diabetes due to noncompressible vessels. Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressures <30 mmHg are suggestive of PAD and an inability to heal foot ulcerations (85). Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for immediate vascular evaluation. Due to the high prevalence of PAD in people with diabetes, the Society

Table 12.1—International Working Group on the Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and No PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • End-stage renal disease	Every 1–3 months

Adapted with permission from Schaper et al. (81). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and person-centered requirements.

for Vascular Surgery and the American Podiatric Medical Association guidelines recommend that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies (84,86). If normal, these should be repeated every 5 years (84).

Education for People With Diabetes

All people with diabetes (and their families), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies (87–89). This education should be provided to all newly diagnosed people with diabetes as part of an annual comprehensive examination and to individuals with high-risk conditions at every visit. Recent studies have shown that while education improves knowledge of diabetic foot problems and self-care of the foot, it does not improve behaviors associated with active participation in their overall diabetes care and to achieve personal health goals (90). Evidence also suggests that while education for people with diabetes and their families is important, the knowledge is quickly forgotten and needs to be reinforced regularly (91).

Individuals considered at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot inspections on a daily basis. Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. People with diabetes should also be educated on the importance of referrals to foot care specialists. A recent study showed that people with diabetes and foot disease lacked awareness of their risk status and why they were being referred to a interprofessional team of foot care specialists. Further, they exhibited a variable degree of interest in learning further about foot complications (92).

Individuals' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Those with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes). Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures (89). Most studies use reduction in peak plantar pressures as an outcome as opposed to ulcer prevention. Certain design features of the orthoses, such as rocker soles and metatarsal accommodations, can reduce peak plantar pressures more significantly than insoles alone. A systematic review, however, showed there was no significant reduction in ulcer incidence after 18 months compared with standard insoles and extra-depth shoes. Further, it was also noted that evidence to prevent first ulcerations was nonexistent (93).

Treatment

Treatment recommendations for people with diabetes will be determined by their risk category. No-risk or low-risk individuals can often be managed with education and self-care. People in the moderate to high risk category should be referred to foot care specialists for further evaluation and regular surveillance as outlined in **Table 12.1**. This includes individuals with LOPS, PAD, and/or structural foot deformities, such as Charcot foot, bunions, or hammertoes. Individuals with any open ulceration or unexplained swelling, erythema, or increased skin temperature should be referred urgently to a foot care specialist or interprofessional team.

Initial treatment recommendations should include daily foot inspection, use of moisturizers for dry, scaly skin, and avoidance of self-care of ingrown nails and calluses. Well-fitted athletic or walking shoes with customized pressure-relieving orthoses should be part of initial recommendations for people with increased plantar pressures (as demonstrated by plantar calluses). Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extra-depth shoes. Those with even more significant deformities, as in Charcot joint disease, may require custom-made footwear.

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require a thorough workup for possible Charcot neuroarthropathy (94). Early diagnosis and treatment of this condition is of paramount importance in preventing deformities and instability that can lead to ulceration and amputation. These individuals require total non–weight-bearing and urgent referral to a foot care specialist for further management. Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings.

There have been a number of developments in the treatment of ulcerations over the years (95). These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and, most recently, topical oxygen therapy (96–98). While there is literature to support many modalities currently used to treat diabetic foot wounds, robust randomized controlled trials (RCTs) are often lacking. However, it is agreed that the initial treatment and evaluation of ulcerations include the following five basic principles of ulcer treatment:

- Offloading of plantar ulcerations
- Debridement of necrotic, nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of physiologic, topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal. In those situations, advanced wound therapy can play a role. When to use advanced wound therapy has been the subject of much discussion, as the therapy is often quite expensive. It has been determined that if a wound fails to show a reduction of 50% or more after 4 weeks of appropriate wound management (i.e., the five basic principles above), consideration should be given to the use of advanced wound therapy (99). Treatment of these chronic wounds is best managed in an interprofessional setting.

Evidence to support advanced wound therapy is challenging to produce and to assess. Randomization of trial participants is difficult, as there are many variables that can affect wound healing. In addition, many RCTs exclude certain cohorts of people, e.g., individuals with chronic renal disease or those on dialysis. Finally, blinding of participants and clinicians is not always possible. Meta-analyses and systematic reviews of observational studies are used to determine the clinical effectiveness of these modalities. Such studies can augment formal RCTs by including a greater variety of participants in various clinical settings who are typically excluded from the more rigidly structured clinical trials.

Advanced wound therapy can be categorized into nine broad categories (95) (**Table 12.2**). Topical growth factors, acellular matrix tissues, and bioengineered cellular therapies are commonly used in offices and wound care centers to expedite healing of chronic, more superficial ulcerations. Numerous clinical reports and retrospective studies have demonstrated the clinical effectiveness of each of these modalities. Over the years, there has been increased evidence to support the use of these modalities. Nonetheless, use of those products or agents with robust RCTs or systematic reviews should generally be preferred over those without level 1 evidence (**Table 12.2**).

Negative-pressure wound therapy was first introduced in the early to mid-1990s. It has become especially useful in wound preparation for skin grafts and flaps and assists in the closure of deep, large wounds (100,101). A variety of types exist in the marketplace and range from electrically powered to mechanically powered in different sizes depending upon the specific wound requirements.

Electrical stimulation, pulsed radiofrequency energy, and extracorporeal shock-wave therapy are biophysical modalities that are believed to upregulate growth factors or cytokines to stimulate wound healing, while low-frequency noncontact ultrasound is used to debride wounds. However, most of the studies advocating the use of these modalities have been retrospective observational or poor-quality RCTs.

Table 12.2—Categories of advanced wound therapies

- Negative-pressure wound therapy
  - Standard electrically powered
  - Mechanically powered
- Oxygen therapies
  - Hyperbaric oxygen therapy
  - Topical oxygen therapy
  - Oxygen-releasing sprays, dressings
- Biophysical
  - Electrical stimulation, diathermy
  - Pulsed electromagnetic fields, pulsed radiofrequency energy
  - Low-frequency noncontact ultrasound
  - Extracorporeal shock wave therapy
- Growth factors
  - Becaplermin: platelet-derived growth factor
  - Fibroblast growth factor
  - Epidermal growth factor
- Autologous blood products
  - Platelet-rich plasma
  - Leukocyte, platelet, fibrin multilayered patches
  - Whole blood clot
- Acellular matrix tissues
  - Xenograft dermis
    - Bovine dermis
  - Xenograft acellular matrices
    - Small intestine submucosa
    - Porcine urinary bladder matrix
    - Ovine forestomach
    - Equine pericardium
    - Fish skin graft
    - Bovine collagen
      - Bilayered dermal regeneration matrix
    - Human dermis products
    - Human pericardium
    - Placental tissues
      - Amniotic tissues/amniotic fluid
      - Umbilical cord
- Bioengineered allogeneic cellular therapies
  - Bilayered skin equivalent (human keratinocytes and fibroblasts)
  - Dermal replacement therapy (human fibroblasts)
- Stem cell therapies
  - Autogenous: bone marrow–derived stem cells
  - Allogeneic: amniotic matrix with mesenchymal stem cells
- Miscellaneous active dressings
  - Hyaluronic acid, honey dressings, etc.
  - Sucrose octasulfate dressing

Adapted with permission from Frykberg and Banks (95).

Hyperbaric oxygen therapy is the delivery of oxygen through a chamber, either individual or multiperson, with the intention of increasing tissue oxygenation to increase tissue perfusion and neovascularization, combat resistant bacteria, and stimulate wound healing. While there had been great interest in this modality being able to expedite healing of chronic DFUs, there has only been one positive RCT published in the last decade that reported increased healing rates at 9 and 12 months compared with control subjects (102). More recent studies with significant design deficiencies and participant dropouts have failed to provide corroborating evidence that hyperbaric oxygen therapy should be widely used for managing nonhealing DFUs (103,104). While there may be some benefit in prevention of amputation in selected chronic neuroischemic ulcers, recent studies have shown no benefit in healing DFUs in the absence of ischemia and/or infection (98,105).

Topical oxygen therapy has been studied rather vigorously in recent years, with several high-quality RCTs and at least five systematic reviews and meta-analyses all supporting its efficacy in healing chronic DFUs at 12 weeks (96,97,106–110) Three types of topical oxygen devices are available, including continuous-delivery, low-constant-pressure, and cyclical-pressure modalities. Importantly, topical oxygen therapy devices provide for home-based therapy rather than the need for daily visits to specialized centers. Very high participation with very few reported adverse events combined with improved healing rates makes this therapy another attractive option for advanced wound care.

If DFUs fail to heal despite appropriate wound care, adjunctive advanced therapies should be instituted and are best managed in an interprofessional manner. Once healed, all individuals should be enrolled in a formal comprehensive prevention program focused on reducing the incidence of recurrent ulcerations and subsequent amputations (80,111,112).

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Recommendations

13.1 Consider the assessment of medical, psychological, functional (self-management abilities), and social domains in older adults with diabetes to provide a framework to determine goals and therapeutic approaches for diabetes management. **B**

13.2 Screen for geriatric syndromes (e.g., cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty) and polypharmacy in older adults with diabetes, as they may affect diabetes self-management and diminish quality of life. **B**

Diabetes is a highly prevalent health condition in the aging population. Over one-quarter of people over the age of 65 years have diabetes and one-half of older adults have prediabetes (1,2). The number of older adults living with these conditions is expected to increase rapidly in the coming decades. Diabetes in older adults is a highly heterogeneous condition. While type 2 diabetes predominates in the older population as in the younger population, improvements in insulin delivery, technology, and care over the last few decades have led to increasing numbers of people with childhood and adult-onset type 1 diabetes surviving and thriving into their later decades. Diabetes management in older adults requires regular assessment of medical, psychological, functional, and social domains. When assessing older adults with diabetes, it is important to accurately categorize the type of diabetes as well as other factors, including diabetes duration, the presence of complications, and treatment-related concerns, such as fear of hypoglycemia. Screening for diabetes complications in older adults should be individualized and periodically revisited, as the results of screening tests may impact treatment goals and therapeutic approaches (3–5). Older adults with diabetes have higher rates of functional disability, accelerated muscle loss, and coexisting illnesses, such as hypertension, chronic kidney disease, coronary heart disease, and stroke, and of premature death than those without diabetes. At the same time, older adults with diabetes

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*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.

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also require greater caregiver support and are at greater risk than other older adults for several common geriatric syndromes such as cognitive impairment, depression, urinary incontinence, injurious falls, persistent pain, and frailty as well as polypharmacy (1). These conditions may impact older adults' diabetes self-management abilities and quality of life if left unaddressed (2,6,7). See Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for the full range of issues to consider when caring for older adults with diabetes.

The comprehensive assessment described above provides a framework to determine goals and therapeutic approaches (8–10), including whether referral for diabetes self-management education is appropriate (when complicating factors arise or when transitions in care occur) or whether the current plan is too complex for the individual's self-management ability or the caregivers providing care (11). Particular attention should be paid to complications that can develop over short periods of time and/or would significantly impair functional status, such as visual and lower-extremity complications. Please refer to the American Diabetes Association (ADA) consensus report "Diabetes in Older Adults" for details (3).

NEUROCOGNITIVE FUNCTION

Recommendation

13.3 Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually, and as appropriate. **B**

Older adults with diabetes are at higher risk of cognitive decline and institutionalization (12,13). The presentation of cognitive impairment ranges from subtle executive dysfunction to memory loss and overt dementia. People with diabetes have higher incidences of all-cause dementia, Alzheimer disease, and vascular dementia than people with normal glucose tolerance (14). Poor glycemic management is associated with a decline in cognitive function (15,16), and longer duration of diabetes is associated with worsening cognitive function. There are ongoing studies evaluating whether lifestyle interventions may help to maintain cognitive function in older adults (17). However, studies examining the effects of diabetes prevention or intensive glycemic and blood pressure management to achieve specific goals have not demonstrated a reduction in brain function decline (18,19). In observational studies as well as post hoc analyses from randomized clinical trials, certain glucose-lowering drugs, such as metformin, thiazolidinediones, and glucagon-like peptide 1 (GLP-1) receptor agonists have shown small benefits on slowing progression of cognitive dysfunction (20). Cardiovascular risk factors are also associated with an increased risk of cognitive decline and dementia. Control of blood pressure and cholesterol lowering with statins have been associated with a reduced risk of incident dementia and are, thus, particularly important in older adults with diabetes.

Recently, the U.S. Food and Drug Administration (FDA) has approved two new anti-amyloid monoclonal antibodies for the treatment of early Alzheimer disease (21). These drugs lower the amyloid burden in the brain and appear to slow cognitive decline in the populations tested. Whether these drugs will be useful in other populations including older adults with diabetes remains to be determined.

Despite the paucity of therapies to prevent or remedy cognitive decline, identifying cognitive impairment early has important implications for diabetes care. The presence of cognitive impairment can make it challenging for clinicians to help people with diabetes reach individualized glycemic, blood pressure, and lipid goals. Cognitive dysfunction may make it difficult for individuals to perform complex self-care tasks (22), such as monitoring glucose and adjusting insulin doses. It can also hinder their ability to appropriately maintain the timing of meals and content of the diet. These factors increase risk for hypoglycemia, which, in turn, can worsen cognitive function. When clinicians are providing care for people with cognitive dysfunction, it is critical to simplify care plans and to facilitate and engage the appropriate support structure to assist individuals in all aspects of care.

Older adults with diabetes should be carefully screened and monitored for cognitive impairment (2). Several simple assessment tools are available to screen for cognitive impairment (22,23), such as the Mini-Mental State Examination (24), Mini-Cog (25), and the Montreal Cognitive Assessment (26), which may help to identify individuals requiring neuropsychological evaluation, particularly when dementia is suspected (i.e., in those experiencing memory loss, a decrease in executive function, and declines in their basic and instrumental activities of daily living). Annual screening is indicated for adults 65 years of age or older for early detection of mild cognitive impairment or dementia (4,27). Screening for cognitive impairment should additionally be considered when an individual presents with a significant decline in clinical status due to increased problems with self-care activities and medication management, such as errors in calculating insulin dose, difficulty counting carbohydrates, skipped meals, skipped insulin doses, and difficulty recognizing, preventing, or treating hypoglycemia. People who screen positive for cognitive impairment should receive diagnostic assessment as appropriate, including referral to a behavioral health professional for formal cognitive/neuropsychological evaluation (28).

HYPOGLYCEMIA

Recommendations

13.4 Because older adults with diabetes have a greater risk of hypoglycemia, especially when treated with hypoglycemic agents (e.g., sulfonylureas, meglitinides, and insulin), than younger adults, episodes of hypoglycemia should be ascertained and addressed at routine visits. **B**

13.5 For older adults with type 1 diabetes, continuous glucose monitoring is recommended to reduce hypoglycemia. **A**

13.6 For older adults with type 2 diabetes on insulin therapy, continuous glucose monitoring should be considered to improve glycemic outcomes and reduce hypoglycemia. **B**

13.7 For older adults with type 1 diabetes, consider the use of automated insulin delivery (AID) systems **A** and other advanced insulin delivery devices such as connected pens **E** to reduce risk of hypoglycemia, based on individual ability and support system.

Older adults are at higher risk of hypoglycemia for many reasons, including erratic meal intake, insulin deficiency necessitating insulin therapy, and progressive renal insufficiency (29). As described above, older adults have higher rates of unidentified cognitive impairment and dementia, leading to difficulties in adhering to complex self-care activities (e.g., glucose monitoring and insulin dose adjustment). Cognitive decline has been associated with increased risk of hypoglycemia, and conversely, severe hypoglycemia has been linked to increased risk of dementia (30–32). Therefore, as discussed in Recommendation 13.3, it is important to routinely screen older adults for cognitive impairment and dementia and discuss findings with the individuals and their caregivers.

People with diabetes and their caregivers should be routinely queried about hypoglycemia (e.g., selected questions from the Diabetes Care Profile) (33) and impaired hypoglycemia awareness as discussed in Section 6, “Glycemic Goals and Hypoglycemia.” Older adults can also be stratified for future risk for hypoglycemia with validated risk calculators (e.g., Kaiser Hypoglycemia Model) (34) and with consideration of hypoglycemia risk factors (**Table 6.5**). An important step to mitigate hypoglycemia risk is to determine whether the person with diabetes is skipping meals or inadvertently repeating doses of their medications. Glycemic goals and pharmacologic treatments may need to be adjusted to minimize the occurrence of hypoglycemic events (2). This recommendation is supported by results from multiple randomized controlled trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Veterans Affairs Diabetes Trial (VADT), which showed that intensive treatment protocols aimed to achieve an A1C $<$6.0% with complex drug plans significantly increased the risk for hypoglycemia requiring assistance compared with standard treatment (35,36). However, these intensive treatment plans included extensive use of insulin and minimal use of GLP-1 receptor agonists, and they preceded the availability of sodium–glucose cotransporter 2 (SGLT2) inhibitors.

Use of Continuous Glucose Monitoring and Advanced Insulin Delivery Devices

For older adults with type 1 diabetes, continuous glucose monitoring (CGM) is a useful approach to predicting and reducing the risk of hypoglycemia (37). In the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial, adults over 60 years of age with type 1 diabetes were randomized to CGM or standard blood glucose monitoring. Over 6 months, use of CGM resulted in a small but statistically significant reduction in time spent with hypoglycemia (glucose level $<$70 mg/dL) compared with standard blood glucose monitoring (adjusted treatment difference -1.9% [-27 min/day]; 95% CI -2.8% to -1.1% [-40 to -16 min/day]; $P < 0.001$) (38,39). Among secondary outcomes, time spent in range between 70 and 180 mg/dL increased by 8% (95% CI 6.0–11.5) and glycemic variability (%CV) decreased. A 6-month extension of the trial demonstrated that these benefits were sustained for up to a year (40). These and other short-term trials are supported by observational data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study indicating that among older adults (mean age 58 years) with long-standing type 1 diabetes, routine CGM and insulin pump use was associated with fewer hypoglycemic events and hyperglycemic excursions and lower A1C levels (41). While the current evidence base for older adults is primarily in type 1 diabetes, the evidence demonstrating the clinical benefits of CGM for people with type 2 diabetes using insulin is growing (42) (see Section 7, “Diabetes Technology”). The DIAMOND (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) study demonstrated that in adults $\geq$60 years of age with either type 1 or type 2 diabetes using multiple daily injections, CGM use was associated with improved A1C and reduced glycemic variability (43). Older adults with physical or cognitive limitations who require monitoring of blood glucose by a surrogate or reside in group homes or assisted living centers are other populations for which CGM may play a useful role.

The availability of accurate CGM devices that can communicate with insulin pumps through Bluetooth has enabled the development of advanced insulin delivery algorithms for pumps. These algorithms fall into two categories: predictive low-glucose suspend algorithms that automatically shut off insulin delivery if a hypoglycemic event is imminent and hybrid closed-loop algorithms that automatically adjust insulin infusion rates based on feedback from a CGM to keep glucose levels in a goal range. Advanced insulin delivery devices have been shown to improve glycemic outcomes in both children and adults with type 1 diabetes. Most trials of these devices have included a broad range of people with type 1 diabetes but relatively few older adults. Recently, two small randomized controlled trials in older adults have been published. The Older Adult Closed Loop (ORACL) trial in 30 older adults (mean age 67 years) with type 1 diabetes found that an automated insulin delivery (AID) strategy was associated with significant improvements in time in range compared with sensor-augmented pump therapy (44). Moreover, they found small but significant decreases in hypoglycemia with the AID strategy. Boughton et al. (45) reported results of an open-label, crossover design clinical trial in 37 older adults ($\geq$60 years) in which 16 weeks of treatment with a hybrid closed-loop advanced insulin delivery system was compared with sensor-augmented pump therapy. They found that hybrid closed-loop insulin delivery improved the proportion of time glucose was in range largely due to decreases in hyperglycemia. In contrast to the ORACL study, no significant differences in hypoglycemia were observed. Both studies enrolled older individuals whose blood glucose was relatively well managed (mean A1C $\sim$7.4%), and both used a crossover design comparing hybrid closed-loop insulin delivery to sensor-augmented pump therapy. These trials provide the first evidence that older individuals with long-standing type 1 diabetes can successfully use advanced insulin delivery technologies to improve glycemic outcomes, as has been seen in younger populations. A recent real world evidence analysis of a Medicare population (n = 4,243, 89% with type 1 diabetes, mean age 67.4 years) also indicated that initiating hybrid closed-loop insulin delivery was associated with improvements in mean glucose and a 10% increase in time in range (46). Use of such technologies should be periodically reassessed, as the burden may outweigh the benefits in those with declining cognitive or functional status.

TREATMENT GOALS

Recommendations

13.8a Older adults with diabetes who are otherwise healthy with few and stable coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C <7.0–7.5% [<53–58 mmol/mol]). C

13.8b Older adults with diabetes and intermediate or complex health are clinically heterogeneous with variable life expectancy. Selection of glycemic goals should be individualized, with less stringent goals (such as A1C <8.0% [<64 mmol/mol]) for those with significant cognitive and/or functional limitations, frailty, severe comorbidities, and a less favorable risk-to-benefit ratio of diabetes medications. C

13.8c Older adults with very complex or poor health receive minimal benefit from stringent glycemic control, and clinicians should avoid reliance on glycemic goals and instead focus on avoiding hypoglycemia and symptomatic hyperglycemia. C

13.9 Screening for diabetes complications should be individualized in older adults with diabetes. Particular attention should be paid to complications that would lead to impairment of functional status or quality of life. C

13.10 Treatment of hypertension to individualized goal levels is indicated in most older adults with diabetes. B

13.11 Treatment of other cardiovascular risk factors should be individualized in older adults with diabetes, considering the time frame of benefit. Lipid-lowering therapy and antiplatelet agents may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials. E

The care of older adults with diabetes is complicated by their clinical, cognitive, and functional heterogeneity and their varied prior experience with disease management. Some older individuals may have developed diabetes years earlier and have significant complications, others are newly diagnosed and may have had years of undiagnosed diabetes with resultant complications, and still, other older adults may have truly recent-onset disease with few or no complications (47). Some older adults with diabetes have other underlying chronic conditions, substantial diabetes-related comorbidity, limited cognitive or physical functioning, or frailty (48,49). Other older individuals with diabetes have little comorbidity and are active.

Life expectancies are highly variable but are often longer than clinicians realize. Multiple prognostic tools for life expectancy for older adults are available (50,51). Notably, the Life Expectancy Estimator for Older Adults with Diabetes (LEAD) tool was developed and validated among older adults with diabetes, and a high risk score was strongly associated with having a life expectancy of <5 years (52). These data may be a useful starting point to inform decisions about selecting less stringent glycemic goals (52,53). Older adults also vary in their preferences for the intensity and mode of glucose management (54). Health care professionals caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals (9,10) (**Table 13.1**). In addition, older adults with diabetes should be assessed for disease treatment and self-management knowledge, health literacy, and mathematical literacy (numeracy) at the onset of treatment. See **Fig. 6.2** for individual/disease-related factors to consider when determining individualized glycemic goals.

A1C may have limitations in those who have medical conditions that impact red blood cell turnover (see Section 2, "Diagnosis and Classification of Diabetes," for additional details on the limitations of A1C) (55). Many conditions associated with increased red blood cell turnover, such as hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, are commonly seen in older adults and can falsely increase or decrease A1C. In these instances, blood glucose monitoring and/or CGM should be used for goal setting (**Table 13.1**). Serum glycated protein assays (fructosamine and glycated albumin) may also be useful for glycemic monitoring in conjunction with other measures (see Section 6, "Glycemic Goals and Hypoglycemia") (56–60).

Older Adults With Good Functional Status and Without Complications

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid management. Older adults who can be expected to live long enough to realize the benefits of long-term intensive diabetes management, who have good cognitive and physical function, and who choose to do so via shared decision-making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes (**Table 13.1**).

As for all people with diabetes, diabetes self-management education and ongoing diabetes self-management support are vital components of diabetes care for older adults and their caregivers. Self-management knowledge and skills should be reassessed when treatment plan changes are made or an individual's functional abilities diminish. In addition, declining or impaired ability to perform diabetes self-care behaviors may be an indication that an older person with diabetes needs a referral for cognitive and physical functional assessment, using age-normalized evaluation tools, as well as help establishing a support structure for diabetes care (3,28).

Older Adults With Complications and Reduced Functionality

Older adults with diabetes categorized as having complex or intermediate health (**Table 13.1**) are heterogeneous with respect to their function and life expectancy (61–63). Based on concepts of competing mortality and time to benefit, some people in this category with shorter life expectancy will have less benefit from glucose lowering and should have less stringent glycemic goals (64). This is especially true for individuals with advanced diabetes complications, life-limiting comorbid illnesses, frailty, or substantial cognitive or functional impairments. These individuals are also more likely to suffer serious adverse effects of therapeutics, such as hypoglycemia (65). However, those with poorly managed diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals should, at a minimum, avoid these consequences. Factors to consider for individualizing glycemic goals are outlined in **Fig. 6.2**. Clinicians should also consider the balance of risks and benefits of an individual's diabetes medications, including disease-specific benefits (such as reducing symptomatic heart failure) and burdens such as hypoglycemia risk, tolerability, difficulties of administration, and financial cost. In addition, attention to oral health, foot

Table 13.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Characteristics and health status of person with diabetes	Rationale	Reasonable A1C goal*	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (<53–58 mmol/mol)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses† or two or more instrumental ADL impairments or mild to moderate cognitive impairment)	Variable life expectancy. Individualize goals, considering: • Severity of comorbidities • Cognitive and functional limitations • Frailty • Risk-to-benefit ratio of diabetes medications • Individual preference	<8.0% (<64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses‡ or moderate to severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit minimal	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

This table represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The characteristic categories are general concepts. Not every individual will clearly fall into a particular category. Consideration of individual and caregiver preferences is an important aspect of treatment individualization. Additionally, an individual's health status and preferences may change over time. ADL, activities of daily living; LTC, long-term care. *A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. †Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. "Multiple" means at least three, but many individuals may have five or more (74). ‡The presence of a single end-stage chronic illness, such as stage 3–4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. Adapted from Kirkman et al. (3).

care, fall prevention, and early detection of depression will improve quality of life.

While **Table 13.1** provides overall guidance for identifying complex and very complex patients, there is not yet global consensus on geriatric patient classification. Ongoing empiric research on the classification of older adults with diabetes based on comorbid illness has repeatedly found three major classes of patients: a healthy, a geriatric, and a cardiovascular class (9,61,66). The geriatric class has the highest prevalence of obesity, hypertension, arthritis, and incontinence, and the cardiovascular class has the highest prevalence of myocardial infarctions, heart failure, and stroke. Compared with the healthy class, the cardiovascular class has the highest risk of frailty and subsequent mortality. Additional research is needed to develop a reproducible classification scheme to distinguish the natural history of disease as well as differential response to glucose management and specific glucose-lowering agents (67).

Vulnerable Older Adults at the End of Life

For people with diabetes receiving palliative care and end-of-life care, the focus should be to avoid hypoglycemia and symptomatic hyperglycemia while reducing the burdens of glycemic management. Thus, as organ failure develops, several agents will have to be deintensified or discontinued. For a dying person, most agents for type 2 diabetes may be removed (68). There is, however, no consensus for the management of type 1 diabetes in this scenario (69). See the section END-OF-LIFE CARE below for additional information.

Beyond Glycemic Management

Although minimizing hyperglycemia may be important in older individuals with diabetes, greater reductions in morbidity and mortality are likely to result from a clinical focus on comprehensive cardiovascular risk factor modification. There is strong evidence from clinical trials of the value of treating hypertension in older adults (70,71), with treatment of hypertension to individualized target levels indicated in most. There is less evidence for lipid-lowering therapy and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames of the clinical trials (72). In the case of statins, the follow-up time of clinical trials ranged from 2 to 6 years. While the time frame of trials can be used to inform treatment decisions, a more specific concept is the time to benefit for a therapy. For statins, a meta-analysis of the previously mentioned trials showed that the time to benefit is 2.5 years (73).

LIFESTYLE MANAGEMENT

Recommendations

13.12 Optimal nutrition and protein intake is recommended for older adults with diabetes; regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training, should be encouraged in all older adults with diabetes who can safely engage in such activities. **B**

13.13 For older adults with type 2 diabetes, overweight/obesity, and capacity to safely exercise, an intensive lifestyle intervention focused on dietary changes, physical activity, and modest weight loss (e.g., 5–7%) should be considered for its benefits on quality of life, mobility and physical functioning, and cardiometabolic risk factor control. **A**

Lifestyle management in older adults should be tailored to frailty status. Diabetes in the aging population is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass, which may result in sarcopenia and/or osteopenia (74,75). Diabetes is also recognized as an independent risk factor for frailty. Frailty is characterized by decline in physical performance and an increased risk of poor health outcomes due to physiologic vulnerability and functional or psychosocial stressors. Inadequate nutritional intake, particularly inadequate protein intake, can increase the risk of sarcopenia and frailty in older adults. Management of frailty in diabetes includes optimal nutrition with adequate protein intake combined with an exercise program that includes aerobic, weight-bearing, and resistance training. The benefits of a structured exercise program (as in the Lifestyle Interventions and Independence for Elders [LIFE] study) in frail older adults include reducing sedentary time, preventing mobility disability, and reducing frailty (76,77). The goal of these programs is not weight loss but enhanced functional status.

For nonfrail older adults with type 2 diabetes and overweight or obesity, an intensive lifestyle intervention designed to reduce weight is beneficial across multiple outcomes. The Look AHEAD (Action for Health in Diabetes) trial is described in Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes.” Look AHEAD specifically excluded individuals with a low functional status. It enrolled people between 45 and 74 years of age and required that they be able to perform a maximal exercise test (78,79). While the Look AHEAD trial did not achieve its primary outcome of reducing cardiovascular events, the intensive lifestyle intervention had multiple clinical benefits that are important to the quality of life of older adults. Benefits included weight loss, improved physical fitness, increased HDL cholesterol, lowered systolic blood pressure, reduced A1C levels, reduced waist circumference, and reduced need for medications (80). Additionally, several subgroups, including participants who lost at least 10% of baseline body weight at year 1, had improved cardiovascular outcomes (81). Risk factor management was improved with reduced utilization of antihypertensive medications, statins, and insulin (82). In age-stratified analyses, older adults in the trial (60 to early 70s) had similar benefits compared with younger people (83,84). In addition, lifestyle intervention produced benefits on aging relevant outcomes such as reductions in multimorbidity and improvements in physical function and quality of life (85–88).

PHARMACOLOGIC THERAPY

Recommendations

13.14 In older adults with type 2 diabetes, medications with low risk of hypoglycemia are preferred, especially for those with hypoglycemia risk factors. **B**

13.15 Overtreatment of diabetes is common in older adults and should be avoided. **B**

13.16a In older adults with diabetes, deintensify hypoglycemia-causing medications (e.g., insulin, sulfonylureas, or meglitinides) or switch to a medication class with low hypoglycemia risk for individuals who are at high risk for hypoglycemia, using individualized glycemic goals. **B**

13.16b In older adults with diabetes, deintensify diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **E**

13.16c Simplification of complex treatment plans (especially insulin) is recommended to reduce the risk of hypoglycemia and polypharmacy and decrease the treatment burden if it can be achieved using the individualized glycemic goals. **B**

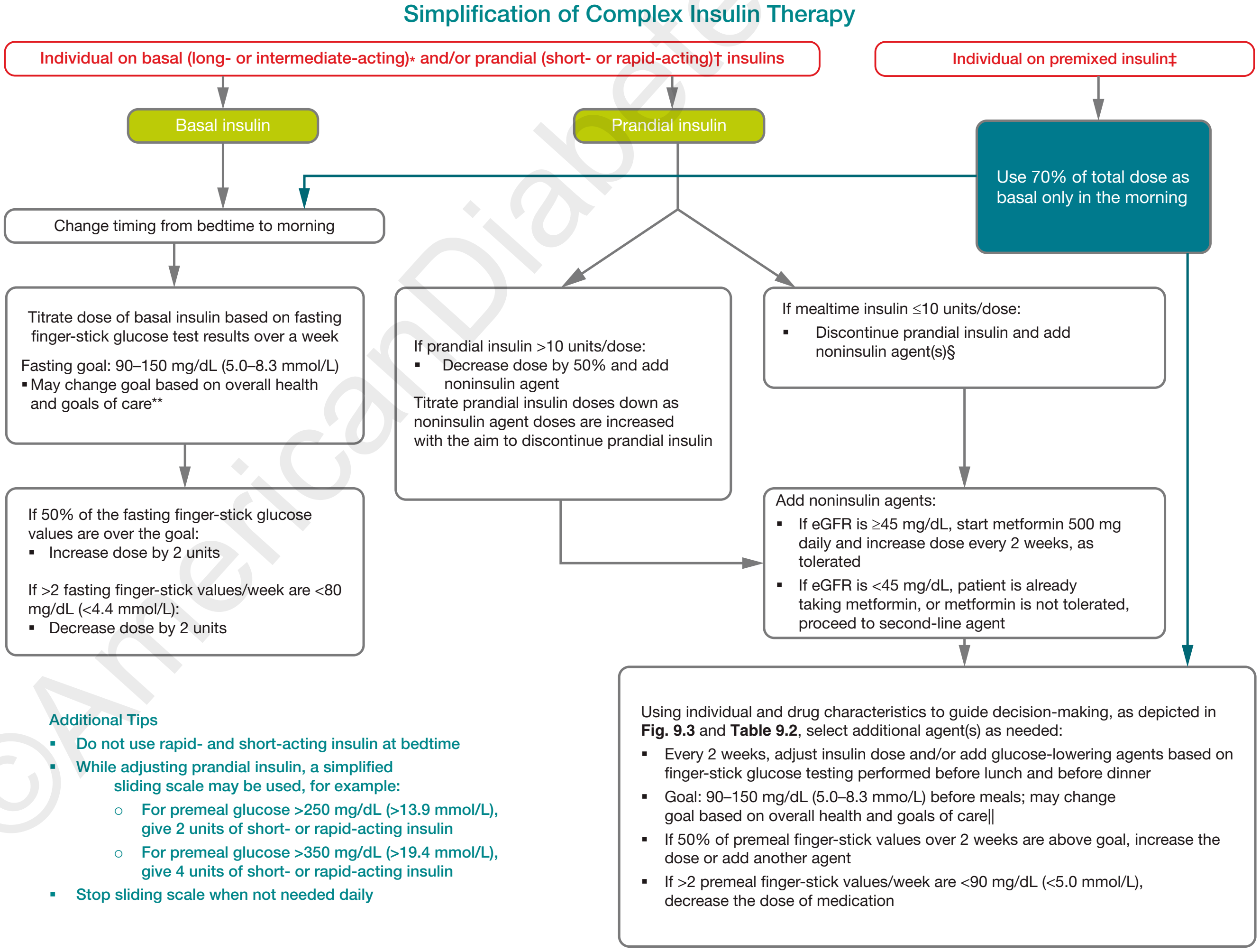
13.16d In older adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment plan should include agents that reduce cardiorenal risk, irrespective of glycemia. **A**

13.17 Consider costs of care and coverage when developing treatment plans in order to reduce risk of cost-related barriers to medication taking and self-management behaviors. **B**

Special care is required in prescribing and monitoring pharmacologic therapies in older adults (89). See **Fig. 9.3** for general recommendations regarding glucose-lowering treatment for adults with type 2 diabetes and **Table 9.2** for person- and drug-specific factors to consider when selecting glucose-lowering agents. Cost may be an especially important consideration, as older adults tend to be on many medications and live on fixed incomes (90). Accordingly, the costs of care and insurance coverage rules should be considered when developing treatment plans to reduce the risk of cost-related barriers to adherence (91,92). See **Table 9.3** and **Table 9.4** for median monthly cost in the U.S. of noninsulin glucose-lowering agents and insulin, respectively. It is important to match complexity of the treatment plan to the self-management ability of older adults with diabetes and their available social and medical support. Many older adults with diabetes struggle to maintain the frequent blood glucose monitoring and insulin injection plans they previously followed, perhaps for many decades, as they develop medical conditions that may impair their ability to follow their treatment plan safely. Individualized glycemic goals should be established (**Fig. 6.2** and **Table 13.1**) and periodically adjusted based on coexisting chronic illnesses, cognitive function, and functional status (2). Intensive glycemic management with medication plans including insulin and sulfonylureas in older adults with complex medical conditions has been identified as overtreatment and found to be very common in clinical practice (93–97). Ultimately, the determination of whether a person is considered overtreated requires an elicitation of the person's perceptions of the current medication burden and preferences for treatments. For those seeking to simplify their diabetes medication plan, deintensification of plans in individuals taking noninsulin glucose-lowering medications can be achieved by either lowering the dose or discontinuing some medications, as long as the individualized glycemic goals are maintained (98). When older adults are found to have an insulin plan with complexity beyond their self-management abilities, lowering the dose of insulin may not be adequate (99). Simplification of the insulin plan to match an individual's self-management abilities and their available social and medical support in these situations has been shown to reduce hypoglycemia and disease-related distress without worsening glycemic outcomes (100–103). **Fig. 13.1** depicts an algorithm that can be used to simplify the insulin plan (102). There are now multiple studies evaluating deintensification protocols in diabetes as well as hypertension, demonstrating that deintensification is safe and possibly beneficial for older adults (98). **Table 13.2** provides examples of and rationale for situations where deintensification and/or insulin plan simplification may be appropriate in older adults.

Metformin

Metformin is the first-line agent for older adults with type 2 diabetes. Recent studies have indicated that it may be used safely in individuals with estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 (104). However, it is contraindicated in those with advanced renal insufficiency and should be used with caution in those with impaired hepatic function or heart failure because of the increased risk of lactic acidosis. Metformin may be temporarily discontinued before procedures including imaging studies using iodinated contrast, during hospitalizations, and when acute illness may compromise renal or liver function. Additionally, metformin



Individual on basal (long- or intermediate-acting)* and/or prandial (short- or rapid-acting)† insulins

Individual on premixed insulin‡

Use 70% of total dose as basal only in the morning

Change timing from bedtime to morning

Titrate dose of basal insulin based on fasting finger-stick glucose test results over a week

Fasting goal: 90–150 mg/dL (5.0–8.3 mmol/L)
- May change goal based on overall health and goals of care**

If 50% of the fasting finger-stick glucose values are over the goal:
- Increase dose by 2 units

If >2 fasting finger-stick values/week are <80 mg/dL (<4.4 mmol/L):
- Decrease dose by 2 units

If prandial insulin >10 units/dose:
- Decrease dose by 50% and add noninsulin agent

Titrate prandial insulin doses down as noninsulin agent doses are increased with the aim to discontinue prandial insulin

If mealtime insulin ≤10 units/dose:
- Discontinue prandial insulin and add noninsulin agent(s)§

Add noninsulin agents:
- If eGFR is ≥45 mg/dL, start metformin 500 mg daily and increase dose every 2 weeks, as tolerated
- If eGFR is <45 mg/dL, patient is already taking metformin, or metformin is not tolerated, proceed to second-line agent

Using individual and drug characteristics to guide decision-making, as depicted in **Fig. 9.3** and **Table 9.2**, select additional agent(s) as needed:
- Every 2 weeks, adjust insulin dose and/or add glucose-lowering agents based on finger-stick glucose testing performed before lunch and before dinner
- Goal: 90–150 mg/dL (5.0–8.3 mmo/L) before meals; may change goal based on overall health and goals of care||
- If 50% of premeal finger-stick values over 2 weeks are above goal, increase the dose or add another agent
- If >2 premeal finger-stick values/week are <90 mg/dL (<5.0 mmol/L), decrease the dose of medication

Additional Tips
- Do not use rapid- and short-acting insulin at bedtime
- While adjusting prandial insulin, a simplified sliding scale may be used, for example:
  - For premeal glucose >250 mg/dL (>13.9 mmol/L), give 2 units of short- or rapid-acting insulin
  - For premeal glucose >350 mg/dL (>19.4 mmol/L), give 4 units of short- or rapid-acting insulin
- Stop sliding scale when not needed daily

Figure 13.1—Algorithm to simplify insulin plans for older adults with type 2 diabetes. eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. †Prandial insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). ‡Premixed insulins: 70/30, 75/25, and 50/50 products. §Examples of noninsulin agents include metformin, sodium–glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide 1 receptor agonists. ||See **Table 13.1**. Adapted with permission from Munshi et al. (102).

Table 13.2—Considerations for treatment plan simplification and deintensification/deprescribing in older adults with diabetes

Characteristics and health status of person with diabetes	Reasonable A1C/ treatment goal	Rationale/considerations	When may medication plan simplification be required?	When may treatment deintensification/ deprescribing be required?
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	<7.0–7.5% (<53–58 mmol/mol)	• Individuals can generally perform complex tasks to maintain good glycemic management when health is stable • During acute illness, individuals may be more at risk for administration or dosing errors that can result in hypoglycemia, falls, fractures, etc.	• If severe or recurrent hypoglycemia occurs in individuals on insulin therapy (regardless of A1C) • If wide glucose excursions are observed • If cognitive or functional decline occurs following acute illness	• If severe or recurrent hypoglycemia occurs in indviduals on noninsulin therapies with high risk of hypoglycemia (regardless of A1C) • If wide glucose excursions are observed • In the presence of polypharmacy
Complex/intermediate (multiple coexisting chronic illnesses or two or more instrumental ADL impairments or mild to moderate cognitive impairment)	<8.0% (<64 mmol/mol)	• Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia • Long-acting medication formulations may decrease pill burden and complexity of medication plan	• If severe or recurrent hypoglycemia occurs in individuals on insulin therapy (even if A1C is appropriate) • If unable to manage complexity of an insulin plan • If there is a significant change in social circumstances, such as loss of caregiver, change in living situation, or financial difficulties	• If severe or recurrent hypoglycemia occurs in individuals on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Community-dwelling individuals receiving care in a skilled nursing facility for short-term rehabilitation	Avoid reliance on A1C, glucose goal 100–200 mg/dL (5.55–11.1 mmol/L)	• Glycemic management is important for recovery, wound healing, hydration, and avoidance of infections • Individuals recovering from illness may not have returned to baseline cognitive function at the time of discharge • Consider the type of support the individual will receive at home	• If treatment plan increased in complexity during hospitalization, it is reasonable, in many cases, to reinstate the prehospitalization medication plan during the rehabilitation	• If the hospitalization for acute illness resulted in weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (LTC or end-stage chronic illnesses or moderate to severe cognitive impairment or two or more ADL impairments)	Avoid reliance on A1C and avoid hypoglycemia and symptomatic hyperglycemia	• No benefits of tight glycemic management in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status	• If on an insulin plan and the individual would like to decrease the number of injections and finger-stick blood glucose monitoring events each day • If the individual has an inconsistent eating pattern	• If on noninsulin agents with a high hypoglycemia risk in the context of cognitive dysfunction, depression, anorexia, or inconsistent eating pattern • If taking any medications without clear benefits
At the end of life	Avoid hypoglycemia and symptomatic hyperglycemia	• Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Caregivers are important in providing medical care and maintaining quality of life	• If there is pain or discomfort caused by treatment (e.g., injections or finger sticks) • If there is excessive caregiver stress due to treatment complexity	• If taking any medications without clear benefits in improving symptoms and/or comfort

Treatment plan simplification refers to changing strategy to decrease the complexity of a medication plan (e.g., fewer administration times and fewer blood glucose checks) and decreasing the need for calculations (such as sliding-scale insulin calculations or insulin-carbohydrate ratio calculations). Deintensification/deprescribing refers to decreasing the dose or frequency of administration of a treatment or discontinuing a treatment altogether. Created using information from Munshi et al. 2016 (102) and 2017 (138). ADL, activities of daily living; LTC, long-term care.

can cause gastrointestinal side effects and a reduction in appetite that can be problematic for some older adults. Reduction or elimination of metformin may be necessary for those experiencing persistent gastrointestinal side effects. For those taking metformin long-term, monitoring for vitamin B12 deficiency should be considered (105).

Thiazolidinediones

Thiazolidinediones, if used at all, should be used very cautiously in older adults on insulin therapy as well as in those with or at risk for heart failure, osteoporosis, falls or fractures, and/or macular edema (106,107). Lower doses of a thiazolidinedione in combination therapy may mitigate these side effects.

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues such as the meglitinides (repaglinide and nateglinide) are associated with hypoglycemia and should be used with caution. If used, sulfonylureas with a shorter duration of action, such as glipizide, are preferred. Glyburide is a longer-acting sulfonylurea and should be avoided in older adults (108).

Incretin-Based Therapies

Oral dipeptidyl peptidase 4 (DPP-4) inhibitors have few side effects and minimal risk of hypoglycemia, but their cost may be a barrier to some older adults. DPP-4 inhibitors do not reduce or increase major adverse cardiovascular outcomes (109). Across the trials of this drug class, there appears to be no interaction by age-group (110–112). A challenge of interpreting the age-stratified analyses of this drug class and other cardiovascular outcomes trials is that while most of these analyses were prespecified, they were not powered to detect differences.

GLP-1 receptor agonists have demonstrated cardiovascular benefits among people with diabetes and established atherosclerotic cardiovascular disease (ASCVD) and those at higher ASCVD risk, and newer trials are expanding our understanding of their benefits in other populations (109). See Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," for a more extensive discussion regarding the specific indications for this class of agents. In a systematic review and meta-analysis of GLP-1 receptor agonist trials, these agents have been found to reduce major adverse cardiovascular events, cardiovascular deaths, stroke, and myocardial infarction to the same degree for people over and under 65 years of age (113). While the evidence for this class of agents for older adults continues to grow, there are a number of practical issues that should be considered specifically for older people. These drugs are injectable agents (with the exception of oral semaglutide) (114), which require visual, motor, and cognitive skills for appropriate administration. Agents with a weekly dosing schedule may however reduce the burden of administration. GLP-1 receptor agonists may also be associated with nausea, vomiting, and diarrhea. Given the gastrointestinal side effects of this class, GLP-1 receptor agonists may not be preferred in older adults who are experiencing unexplained weight loss or have suspected gastroparesis or recurrent gastrointestinal problems.

Recently, tirzepatide, a novel dual-acting GIP and GLP-1 receptor coagonist, was approved by the FDA for the treatment of type 2 diabetes. Tirzepatide is administered as a once-weekly subcutaneous injection. In phase 3 trials, tirzepatide decreased A1C and weight—generally to a greater extent than other glucose-lowering drugs including semaglutide and insulin—with no significant differences in the safety or efficacy in older compared with younger individuals (115).

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors are administered orally, which may be convenient for older adults with diabetes. In those with established ASCVD, these agents have shown cardiovascular benefits (109). This class of agents has also been found to be beneficial for people with heart failure and to slow the progression of chronic kidney disease. See Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," for a more extensive discussion regarding the indications for this class of agents. Stratified analyses of the trials of this drug class indicate that older adults have similar or greater benefits than younger people (116–118). While understanding of the clinical benefits of this class is evolving, side effects such as volume depletion, urinary tract infections, and worsening urinary incontinence may be more common among older people, and these drugs should be used with caution in individuals who depend on caregivers for adequate fluid intake or who have recurrent urinary tract infections.

Insulin Therapy

The use of insulin therapy requires that individuals or their caregivers have good visual and motor skills and cognitive ability. Insulin therapy relies on the ability of the older person with diabetes to administer insulin on their own or with the assistance of a caregiver. Insulin doses should be titrated to meet individualized glycemic goals and to avoid hypoglycemia.

Once-daily basal insulin injection therapy is associated with minimal side effects and may be a reasonable option in many older adults (119). When choosing a basal insulin, long-acting insulin analogs have been found to be associated with a lower risk of hypoglycemia compared with NPH insulin in the Medicare population. Multiple daily injections of insulin may be too complex for an older person with advanced diabetes complications, life-limiting coexisting chronic illnesses, or limited functional status. **Fig. 13.1** provides a potential approach to insulin plan simplification.

Other Factors to Consider

The needs of older adults with diabetes and their caregivers should be evaluated to construct a tailored care plan. Impaired social support and reduced access to long-term services and support may reduce these individuals' quality of life and increase the risk of functional dependency (7). The person's living situation must be considered as it may affect diabetes management and support needs. Social and instrumental support networks (e.g., adult children and caretakers) that provide instrumental or emotional support for older adults with diabetes should be included in diabetes management discussions and shared decision-making.

The need for ongoing support of older adults becomes even greater when transitions to acute care and long-term care (LTC) become necessary. Unfortunately, these transitions can lead to discontinuity in goals of care, errors in dosing, and changes in nutrition and activity (120). Older adults in assisted living facilities may not have support to administer their own medications, whereas those living in a nursing home (community living centers) may rely on first-line caregivers including nursing and care professionals with variable clinical expertise. Those receiving palliative care (with or without hospice) may require an approach that emphasizes comfort and symptom management while deemphasizing strict metabolic and blood pressure management.

SPECIAL CONSIDERATIONS FOR OLDER ADULTS WITH TYPE 1 DIABETES

Due in part to the success of modern diabetes management, people with type 1 diabetes are living longer, and the population of these people over 65 years of age is growing (121–123). Many of the recommendations in this section regarding a comprehensive geriatric assessment and personalization of goals and treatments are directly applicable to older adults with type 1 diabetes; however, this population has unique challenges and requires distinct treatment considerations (124). Insulin is an essential life-preserving therapy for people with type 1 diabetes, unlike for those with type 2 diabetes. To avoid diabetic ketoacidosis, older adults with type 1 diabetes need some form of basal insulin even when they are unable to ingest meals. Insulin may be delivered through an insulin pump or injections. CGM is approved for use by Medicare and can play a critical role in improving A1C, reducing glycemic variability, and reducing risk of hypoglycemia (43) (see Section 7, “Diabetes Technology,” and Section 9, “Pharmacologic Approaches to Glycemic Treatment”). In older people with type 1 diabetes, administration of insulin may become more difficult as complications, cognitive impairment, and functional impairment arise. This increases the importance of caregivers in the lives of these individuals. Many older people with type 1 diabetes require placement in LTC settings (i.e., nursing homes and skilled nursing facilities), and unfortunately staff in these settings are less familiar with CGM devices, insulin pumps, or advanced insulin delivery devices. Some staff may be less knowledgeable about the differences between type 1 and type 2 diabetes. In these instances, the individual or the person’s family may be more familiar with their diabetes management plan than the staff or health care professionals. Education of relevant support staff and health care professionals in rehabilitation and LTC settings regarding insulin dosing and use of pumps and CGM is recommended as part of general diabetes education (see Recommendations 13.18 and 13.19).

TREATMENT IN SKILLED NURSING FACILITIES AND NURSING HOMES

Recommendations

13.18 Consider diabetes education/training (including that for CGM devices, insulin pumps, and advanced insulin delivery systems) for the staff of long-term care and rehabilitation facilities to improve the management of older adults with diabetes. **E**

13.19 People with diabetes residing in long-term care facilities need careful assessment to establish individualized glycemic goals and to make appropriate choices of glucose-lowering agents and devices (including CGM devices, insulin pumps, and advanced insulin delivery systems) based on their clinical and functional status. **E**

Management of diabetes in the LTC setting is unique. Individualization of health care is important for all people with diabetes; however, practical guidance is needed for health care professionals as well as the LTC staff and caregivers (125). Training should include diabetes detection and institutional quality assessment. LTC facilities should develop their own policies and procedures for prevention, recognition, and management of hypoglycemia. With the increased longevity of populations, the care of people with diabetes and its complications in LTC is an area that warrants greater study.

Resources

Staff of LTC facilities should receive appropriate diabetes education to improve the management of older adults with diabetes. Treatments for each person with diabetes should be individualized. Special management considerations include the need to avoid both hypoglycemia and the complications of hyperglycemia (2,126). For more information, see the ADA position statement “Management of Diabetes in Long-term Care and Skilled Nursing Facilities” (125).

Nutritional Considerations

An older adult residing in an LTC facility may have irregular and unpredictable meal consumption, undernutrition, anorexia, and impaired swallowing. Furthermore, therapeutic diets may inadvertently lead to decreased food intake and contribute to unintentional weight loss and undernutrition. Meals tailored to a person’s culture, preferences, and personal goals may increase quality of life, satisfaction with meals, and nutrition status (127). It may be helpful to give insulin after meals to ensure that the dose is appropriate for the amount of carbohydrate the individual consumed in the meal.

Hypoglycemia

Older adults with diabetes in LTC are especially vulnerable to hypoglycemia. They have a disproportionately high number of clinical complications and comorbidities that can increase hypoglycemia risk: impaired cognitive and renal function, slowed hormonal regulation and counterregulation, suboptimal hydration, variable appetite and nutritional intake, polypharmacy, and slowed intestinal absorption (128). Oral agents may achieve glycemic outcomes similar to basal insulin in LTC populations (93,129). CGM may be a useful approach to monitoring for hypoglycemia among individuals treated with insulin in LTC, but the data are limited.

Another consideration for the LTC setting is that unlike in the hospital setting, health care professionals are not required to evaluate patients daily. According to federal guidelines, assessments should be done at least every 30 days for the first 90 days after admission and then at least once every 60 days. Although in practice patients may actually be seen more frequently, the concern is that these individuals may have uncontrolled glucose levels or wide excursions without the practitioner being notified. Health care professionals may adjust treatment plans by telephone, fax, or in person directly at the LTC facilities, provided they are given timely notification of blood glucose management issues from a standardized alert system.

The following alert strategy could be considered:

1. **Call health care professional immediately** in cases of low blood glucose levels (<70 mg/dL [<3.9 mmol/L]). However, treatment of hypoglycemia should not be delayed. A health care

professional should also be called if two or more blood glucose values >250 mg/dL are observed within a 24-h period and are accompanied by a significant change in status.

2. Call as soon as possible when
    a) glucose values are 70–100 mg/dL (3.9–5.6 mmol/L) (treatment plan may need to be adjusted),
    b) glucose values are consistently >250 mg/dL (>13.9 mmol/L) within a 24-h period,
    c) glucose values are consistently >300 mg/dL (>16.7 mmol/L) over 2 consecutive days,
    d) any reading is too high for the glucose monitoring device, or
    e) the person is sick, with vomiting, symptomatic hyperglycemia, or poor oral intake.

END-OF-LIFE CARE

Recommendations

13.20 When palliative care is needed in older adults with diabetes, health care professionals should initiate conversations with people with diabetes and their care partners regarding the goals and intensity of care. Strict glucose and blood pressure management are not necessary, and simplification of medication plans can be considered. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. **E**

13.21 Overall comfort, prevention of distressing symptoms, and preservation of quality of life and dignity are primary goals for diabetes management at the end of life. **C**

The management of the older adult at the end of life receiving palliative medicine or hospice care is a unique situation. Overall, palliative medicine promotes comfort, symptom management and prevention (pain, hypoglycemia, hyperglycemia, and dehydration), and preservation of dignity and quality of life in older adults with limited life expectancy (126,130). In the setting of palliative care, health care professionals should initiate conversations with people with diabetes and their care partners regarding the goals and intensity of diabetes care; strict glucose and blood pressure management may not be consistent with achieving comfort and quality of life. Avoidance of severe hypertension and hyperglycemia aligns with the goals of palliative care. In a multicenter trial, withdrawal of statins among people with diabetes in palliative care was found to improve quality of life (131–133). The evidence for the safety and efficacy of deintensification protocols in older adults is growing for both glucose and blood pressure management (97,134) and is clearly relevant for palliative care. An individual has the right to refuse testing and treatment, whereas health care professionals may consider withdrawing treatment and limiting diagnostic testing, including a reduction in the frequency of blood glucose monitoring (135,136). Glycemic goals should aim to prevent hypoglycemia and hyperglycemia. Treatment interventions need to be mindful of quality of life. Careful monitoring of oral intake is warranted. The decision process may need to involve the individual, family, and caregivers, leading to a care plan that is both convenient and effective for the goals of care (137). The pharmacologic therapy may include oral agents as first line, followed by a simplified insulin plan. If needed, basal insulin can be implemented, accompanied by oral agents and without rapid-acting insulin. Agents that can cause gastrointestinal symptoms such as nausea or excess weight loss may not be good choices in this setting. As symptoms progress, some agents may be slowly tapered and discontinued.

Different categories have been proposed for diabetes management in those with advanced disease (68).

1. A stable individual: Continue with the person's previous medication plan, with a focus on *1*) the prevention of hypoglycemia and *2*) the management of hyperglycemia using blood glucose testing, keeping levels below the renal threshold of glucose, and hyperglycemia-mediated dehydration. There is no role for A1C monitoring.
2. An individual with organ failure: Preventing hypoglycemia is of greatest significance. Dehydration must be prevented and treated. In people with type 1 diabetes, insulin administration may be reduced as the oral intake of food decreases but should not be stopped. For those with type 2 diabetes, agents that may cause hypoglycemia should be reduced in dose. The main goal is to avoid hypoglycemia, allowing for glucose values in the upper level of the desired goal range.
3. A dying individual: For people with type 2 diabetes, the discontinuation of all medications may be a reasonable approach, as these individuals are unlikely to have any oral intake. In people with type 1 diabetes, there is no consensus, but a small amount of basal insulin may maintain glucose levels and prevent acute hyperglycemic complications.

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14. Children and Adolescents: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

The management of diabetes in children and adolescents (individuals <18 years of age) cannot simply be derived from care routinely provided to adults with diabetes. The epidemiology, pathophysiology, developmental considerations, and response to therapy in pediatric diabetes are often different from those of adult diabetes. There are also differences in recommended care for children and adolescents with type 1 diabetes, type 2 diabetes, and other forms of pediatric diabetes. This section is divided into two major parts: the first part addresses care for children and adolescents with type 1 diabetes, and the second part addresses care for children and adolescents with type 2 diabetes. Monogenic diabetes (neonatal diabetes and maturity-onset diabetes of the young [MODY]) and cystic fibrosis–related diabetes, which are often present in youth, are discussed in Section 2, "Diagnosis and Classification of Diabetes." **Table 14.1*A*** and **Table 14.1*B*** provide an overview of the recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes and type 2 diabetes, respectively. In addition to comprehensive diabetes care, youth with diabetes should receive age-appropriate and developmentally appropriate pediatric care, including immunizations as recommended by the Centers for Disease Control and Prevention (CDC) (1). To ensure continuity of care as an adolescent with diabetes becomes an adult, guidance is provided at the end of this section on the transition from pediatric to adult diabetes care.

Due to the nature of pediatric clinical research, the recommendations for children and adolescents with diabetes are less likely to be based on clinical trial evidence. However, expert opinion and a review of available and relevant experimental data are summarized in the American Diabetes Association (ADA) position statements "Type 1 Diabetes in Children and Adolescents" (2) and "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3). Finally, other sections in the Standards of Care may have recommendations that apply to youth with diabetes and are referenced in the narrative of this section.

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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Table 14.1*A*—Recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes

	Thyroid disease	Celiac disease	Hypertension	Nephropathy	Retinopathy	Neuropathy	Dyslipidemia
Corresponding recommendations	14.28 and 14.29	14.30–14.32	14.33–14.36	14.42 and 14.43	14.44–14.46	14.47	14.37–14.41
Method	Thyroid-stimulating hormone; consider antithyroglobulin and antithyroid peroxidase antibodies	IgA tTG if total IgA normal; IgG tTG and deamidated gliadin antibodies if IgA deficient	Blood pressure monitoring	Albumin-to-creatinine ratio; random sample acceptable initially	Dilated fundoscopy or retinal photography	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes	Lipid profile, nonfasting acceptable initially
When to start	Soon after diagnosis	Soon after diagnosis	At diagnosis	Puberty or ≥10 years old, whichever is earlier, and diabetes duration of 5 years	Puberty or ≥11 years old, whichever is earlier, and diabetes duration of 3–5 years	Puberty or ≥10 years old, whichever is earlier, and diabetes duration of 5 years	Soon after diagnosis; preferably after glycemia has improved and ≥2 years old
Follow-up frequency	Every 1–2 years if thyroid antibodies negative; more often if symptoms develop or presence of thyroid antibodies	Within 2 years and then at 5 years after diagnosis; sooner if symptoms develop	Every visit	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months	If normal, every 2 years; consider less frequently (every 4 years) if A1C <8% and eye professional agrees	If normal, annually	If LDL <100 mg/dL, repeat at 9–11 years old; then, if <100 mg/dL, every 3 years
Goal	NA	NA	<90th percentile for age, sex, and height; if ≥13 years old, <120/80 mmHg	Albumin-to-creatinine ratio <30 mg/g	No retinopathy	No neuropathy	LDL <100 mg/dL
Treatment	Appropriate treatment of underlying thyroid disorder	After confirmation, start gluten-free diet	Lifestyle modification for elevated blood pressure (90th to <95th percentile for age, sex, and height or, if ≥13 years old, 120–129/<80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥95th percentile for age, sex, and height or, if ≥13 years old, ≥130/80 mmHg)	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; treatment per ophthalmology	Optimize glycemia; referral to neurology	If abnormal, optimize glycemia and medical nutrition therapy; if after 6 months LDL >160 mg/dL or >130 mg/dL with cardiovascular risk factor(s), initiate statin therapy (for those aged >10 years)*

ARB, angiotensin receptor blocker; NA, not applicable; tTG, tissue transglutaminase. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

Table 14.1*B*—Recommendations for screening and treatment of complications and related conditions in pediatric type 2 diabetes

	Hypertension	Nephropathy	Neuropathy	Retinopathy	Dyslipidemia	Nonalcoholic fatty liver disease	Obstructive sleep apnea	Polycystic ovarian syndrome (for adolescent femaleindividuals)
Corresponding recommendations	14.74–14.77	14.78–14.83	14.84 and 14.85	14.86–14.89	14.96–14.100	14.90 and 14.91	14.92	14.93 and 14.94
Method	Blood pressure monitoring	Albumin-to-creatinine ratio; random sample acceptable initially	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes	Dilated fundoscopy	Lipid profile	AST and ALT measurement	Screening for symptoms	Screening for symptoms; laboratory evaluation if positive symptoms
When to start	At diagnosis	At diagnosis	At diagnosis	At/soon after diagnosis	Soon after diagnosis, preferably after glycemia has improved	At diagnosis	At diagnosis	At diagnosis
Follow-up frequency	Every visit	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months	If normal, annually	If normal, annually	Annually	Annually	Every visit	Every visit
Goal	<90th percentile for age, sex, and height; if ≥13 years old, <130/80 mmHg	<30 mg/g	No neuropathy	No retinopathy	LDL <100 mg/dL, HDL >35 mg/dL, triglycerides <150 mg/dL	NA	NA	NA
Treatment	Lifestyle modification for elevated blood pressure (90th to <95th percentile for age, sex, and height or, if ≥13 years old, 120–129/<80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥95th percentile for age, sex, and height or, if ≥13 years, ≥130/80 mmHg)	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; referral to neurology	Optimize glycemia; treatment per ophthalmology	If abnormal, optimize glycemia and medical nutrition therapy; if LDL >130 mg/dL after 6 months, initiate statin therapy (for those aged >10 years)*; if triglycerides >400 mg/dL fasting or >1,000 mg/dL nonfasting, begin fibrate	Refer to gastroenterology for persistently elevated or worsening transaminases	If positive symptoms, refer to sleep specialist and polysomnogram	If no contraindications, oral contraceptive pills; medical nutrition therapy; metformin

ARB, angiotensin receptor blocker; NA, not applicable; tTG, tissue transglutaminase. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

TYPE 1 DIABETES

Type 1 diabetes is the most common form of diabetes in youth (4), although data suggest that it accounts for a large proportion of cases diagnosed in adult life (5). The health care professional must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of diabetic ketoacidosis (DKA) (6,7). Attention to family dynamics, developmental stages, and physiologic differences related to sexual maturity is essential in developing and implementing an optimal diabetes treatment plan (8).

An interprofessional team trained in pediatric diabetes management and sensitive to the challenges of children and adolescents with type 1 diabetes and their families should provide diabetes-specific care for this population. It is essential that diabetes self-management education and support, medical nutrition therapy, and psychosocial/behavioral support be provided at diagnosis and regularly thereafter in a developmentally appropriate format that builds on prior knowledge by a team of health care professionals experienced with the biological, educational, nutritional, behavioral, and emotional needs of the growing child and family. The diabetes team, taking into consideration the youth's developmental and psychosocial needs, should ask about and discuss diabetes management responsibilities with youth and parents/caregivers on an ongoing basis.

Diabetes Self-Management Education and Support

Recommendation

14.1 Youth with type 1 diabetes and their parents/caregivers (for individuals aged <18 years) should receive culturally sensitive and developmentally appropriate individualized diabetes self-management education and support according to national standards at diagnosis and routinely thereafter. **B**

Self-management in pediatric diabetes involves both the youth and their parents/adult caregivers. No matter how sound the medical plan is, it can only be effective if the family and/or affected individuals are able to implement it. Family involvement is a vital component of optimal diabetes management throughout childhood and adolescence. As parents/caregivers are critical to diabetes self-management in youth, diabetes care requires an approach that places the youth and their parents/caregivers at the center of the care model. The pediatric diabetes care team must be capable of evaluating the educational, behavioral, emotional, and psychosocial factors that impact the implementation of a treatment plan and must work with the youth and family to overcome barriers or redefine goals as appropriate. Diabetes self-management education and support requires periodic reassessment, especially as the youth grows, develops, and acquires the need and desire for greater independent self-care skills. The pediatric diabetes team should work with the youth and their parents/caregivers to ensure there is not a premature transfer of self-management tasks to the youth during this time. In addition, it is necessary to assess the educational needs and skills of, and provide training to, daycare workers, school nurses, and school personnel who are responsible for the care and supervision of the child with diabetes (2,9,10).

Nutrition Therapy

Recommendations

14.2 Individualized medical nutrition therapy is recommended for youth with type 1 diabetes as an essential component of the overall treatment plan. **A**

14.3 Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is a key component to optimizing glycemic management. **B**

14.4 Meal composition impacts postprandial glucose excursions. Education on the impact of high-fat and high-protein meals and the adjustment of insulin dosing is necessary. **A**

14.5 Comprehensive nutrition education at diagnosis, with at least annual updates and as needed, by an experienced registered dietitian nutritionist is recommended to assess caloric and nutrition intake in relation to weight status and cardiovascular disease risk factors and to inform macronutrient choices. **E**

Nutrition management should be individualized: family habits, food preferences, religious or cultural needs, finances, schedules, physical activity, and the youth's and family's abilities in numeracy, literacy, and self-management should be considered. Visits with a registered dietitian nutritionist should include assessment for changes in food preferences over time, access to food, growth, and development, weight status, cardiovascular risk, and potential for disordered eating. Following recommended nutrition plans is associated with better glycemic outcomes in youth with type 1 diabetes (11).

Although carbohydrate content is the primary variable for calculation of meal insulin dose, it is well known that meals with higher content of fat and protein can cause early hypoglycemia and delayed postprandial excursion. Some adjustments in insulin dosing, including an increase in the calculated dose as well as a split dose, will improve postprandial glucose management (12–28).

Physical Activity and Exercise

Recommendations

14.6 Physical activity is recommended for all youth with type 1 diabetes with the goal of 60 min of moderate- to vigorous-intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week. **C**

14.7 Frequent glucose monitoring before, during, and after exercise, via blood glucose meter or continuous glucose monitoring (CGM), is important to prevent, detect, and treat hypoglycemia and hyperglycemia associated with exercise. **C**

14.8 Youth and their parents/caregivers should receive education on goals and management of glycemia before, during, and after physical activity, individualized according to the type and intensity of the planned physical activity. **E**

14.9 Youth and their parents/caregivers should be educated on strategies to prevent hypoglycemia during, after, and overnight following physical activity and exercise, which may include reducing prandial insulin dosing for the meal/snack preceding (and, if needed, following) exercise, reducing basal insulin doses, increasing carbohydrate intake, eating bedtime snacks, and/or using CGM. Treatment for hypoglycemia should be accessible before, during, and after engaging in activity. **C**

Physical activity and structured exercise positively impact metabolic and psychological health in children with type 1 diabetes (29). While it affects insulin sensitivity, physical fitness, strength building, weight management, social interaction, mood, self-esteem building, and the creation of healthful habits for adulthood, it also has the potential to cause both hypoglycemia and hyperglycemia.

See below for strategies to mitigate hypoglycemia risk and minimize hyperglycemia associated with exercise. For an in-depth discussion, see reviews and guidelines (30–32).

Overall, it is recommended that youth participate in 60 min of moderate-intensity (e.g., brisk walking or dancing) to vigorous-intensity (e.g., running or jumping rope) aerobic activity daily, including resistance and flexibility training (33). Although uncommon in the pediatric population, youth should be medically evaluated for comorbid conditions or diabetes complications that may restrict participation in an exercise program. As hyperglycemia can occur before, during, and after physical activity, it is important to ensure that the elevated glucose level is not related to insulin deficiency that would lead to worsening hyperglycemia with exercise and ketosis risk. Intense activity should be postponed with marked hyperglycemia (glucose $\geq$350 mg/dL [$\geq$19.4 mmol/L]), moderate to large urine ketones, and/or β-hydroxybutyrate (B-OHB) >1.5 mmol/L. Caution may be needed when B-OHB levels are $\geq$0.6 mmol/L (11,30).

The prevention and treatment of hypoglycemia associated with physical activity include decreasing the prandial insulin for the meal/snack before exercise and/or increasing food intake. Youth on insulin pumps without automated insulin delivery (AID) can lower basal rates by ~10–50% or more or suspend for 1–2 h during exercise (34). Decreasing basal rates or long-acting insulin doses by ~20% after exercise may reduce delayed exercise-induced hypoglycemia (35). Accessible rapid-acting carbohydrates and frequent blood glucose monitoring before, during, and after exercise, with or without continuous glucose monitoring (CGM), maximize safety with exercise. The use of AID systems may improve time in range (TIR) (70–180 mg/dL) during exercise, and youth can use brand-specific settings that are more conservative or increase the glycemic goal to prevent hypoglycemia (36).

Blood glucose goals prior to physical activity and exercise should be 126–180 mg/dL (7.0–10.0 mmol/L) but should be individualized based on the type, intensity, and duration of activity (30,32). Consider additional carbohydrate intake during and/or after exercise, depending on the duration and intensity of physical activity, to prevent hypoglycemia. For low- to moderate-intensity aerobic activities (30–60 min), and if the youth is fasting, 10–15 g of carbohydrate may prevent hypoglycemia (32). After insulin boluses (relative hyperinsulinemia), consider 0.5–1.0 g of carbohydrates/kg per hour of exercise (~30–60 g), which is similar to carbohydrate requirements to optimize performance in athletes without type 1 diabetes (37–39).

In addition, obesity is as common in youth with type 1 diabetes as in those without diabetes. It is associated with a higher frequency of cardiovascular risk factors, and it disproportionately affects racial/ethnic minorities in the U.S. (40–44). Therefore, diabetes health care professionals should monitor weight status and encourage a healthy eating pattern, physical activity, and healthy weight as key components of pediatric type 1 diabetes care.

School and Child Care

As a large portion of a youth's day is spent in school and/or day care, training of school or day care personnel to provide care in accordance with the child's individualized diabetes medical management plan is essential for optimal diabetes management and safe access to all school or day care–sponsored opportunities (10,45,46). In addition, federal and state laws require schools, day care facilities, and other entities to provide needed diabetes care to enable the child to safely access the school or day care environment. Refer to the ADA position statements "Diabetes Care in the School Setting" (10) and "Care of Young Children With Diabetes in the Childcare and Community Setting" (46) and the ADA's Safe at School website (diabetes.org/resources/know-your-rights/safe-at-school-state-laws) for additional details.

Psychosocial Care

Recommendations

14.10 At diagnosis and during routine follow-up care, screen youth with type 1 diabetes for psychosocial concerns (e.g., diabetes distress, depressive symptoms, and disordered eating), family factors, and behavioral health concerns that could impact diabetes management with age-appropriate standardized and validated tools. Refer to a qualified behavioral health professional, preferably experienced in childhood diabetes, when indicated. **B**

14.11 Behavioral health professionals should be considered integral members of the pediatric diabetes interprofessional team. **E**

14.12 Encourage developmentally appropriate family involvement in diabetes management tasks for children and adolescents, recognizing that premature or unsupportive transfer of diabetes care responsibility to the youth can contribute to diabetes distress, lower engagement in diabetes self-management behaviors, and deterioration in glycemia. **A**

14.13 Health care professionals should screen for food security, housing stability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. **E**

14.14 Health care professionals should consider asking youth and their parents/caregivers about social adjustment (peer relationships) and school performance to determine whether further intervention is needed. **B**

14.15 Offer adolescents time by themselves with their health care professional(s) starting at age 12 years or when developmentally appropriate. **E**

14.16 Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all individuals of childbearing potential. **A**

Rapid and dynamic cognitive, developmental, and emotional changes occur during childhood, adolescence, and emerging adulthood. Diabetes management during childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial status, social determinants of health, and diabetes distress in the youth and the parents/caregivers during routine diabetes visits (47–55). It is important to consider the impact of diabetes on quality of life as well as the development of behavioral health problems related to diabetes distress, fear of hypoglycemia (and hyperglycemia), symptoms of anxiety, disordered eating behaviors and eating disorders, and symptoms of depression (50,56). Consider screening youth for diabetes distress, generally starting at 7 or 8 years of age (56), using validated tools for youth and their parents/caregivers (57). Consider screening for depression and disordered eating behaviors using available screening tools (58,59). Early detection of depression, anxiety, disordered eating, and learning disabilities can facilitate effective treatment options and help minimize adverse effects on diabetes management and disease outcomes (50,56). When psychological symptoms are identified, referral to a behavioral health professional, ideally with experience in pediatric diabetes, may be warranted. Such professionals can provide individualized, evidence-based behavioral health care services, including cognitive-behavioral, mindfulness-based, and other interventions (60), to improve psychosocial functioning in youth with type 1 diabetes (61–63).

The complexities of diabetes management require ongoing parental involvement in care throughout childhood and adolescence. Developmentally appropriate, supportive family teamwork between the growing youth and parent can help maintain engagement in self-management behaviors and reduce deterioration in glycemia (64,65). It is appropriate to inquire about diabetes-specific family relationships, including family teamwork and conflict, during visits; health care professionals can both help families negotiate a plan and refer to an appropriate behavioral health professional for more in-depth support (66). Such professionals can conduct further assessment and deliver evidence-based behavioral interventions to support developmentally appropriate, collaborative family involvement in diabetes self-management (61,63). Monitoring of social adjustment (peer relationships) and school performance can facilitate both well-being and academic achievement (67). Diabetes management and glycemic levels may be related to academic progress and students' functioning in the school setting, which highlights the need for appropriate accommodations and access to diabetes-related support in school (68).

Shared decision-making with youth regarding the adoption of management plan components and self-management behaviors can improve diabetes self-efficacy, participation in diabetes care, and metabolic outcomes (41,69). Although cognitive abilities vary, the ethical position often adopted is the "mature minor rule," whereby children after age 12 or 13 years who appear to be "mature" have the right to consent or withhold consent to general medical treatment, except in cases in which refusal would significantly endanger health (70).

Beginning at the onset of puberty or at diagnosis of diabetes, all individuals with childbearing potential should receive education about the risks of fetal malformations associated with elevated A1C and the use of effective contraception to prevent unplanned pregnancy. Preconception counseling using developmentally appropriate educational and behavioral strategies enables individuals of childbearing potential to make well-informed decisions (71). Preconception counseling resources tailored for adolescents are available at no cost through the ADA (72). Refer to the ADA position statement "Psychosocial Care for People With Diabetes" for further details (56).

Youth with type 1 diabetes have an increased risk of disordered eating behavior as well as clinical eating disorders, with serious short-term and long-term negative effects on diabetes outcomes and health in general. It is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight management in type 1 diabetes (73) using tools such as the Diabetes Eating Problems Survey-Revised (DEPS-R) to allow for early diagnosis and intervention (59,74–76). Given the complexity of treating disordered eating behaviors, collaboration between the diabetes health care team and a behavioral health professional, ideally with expertise in disordered eating behaviors and diabetes, is recommended.

The presence of a behavioral health professional on pediatric interprofessional teams highlights the importance of attending to the psychosocial issues of diabetes. These psychosocial factors are significantly related to self-management difficulties, elevated A1C, reduced quality of life, and higher rates of acute and chronic diabetes complications.

Glycemic Monitoring, Insulin Delivery, and Goals

Recommendations

14.17 All youth with type 1 diabetes should monitor glucose levels multiple times daily (up to 6–10 times/day by blood glucose meter or CGM), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as physical activity, driving, or the presence of symptoms of hypoglycemia. **B**

14.18 Real-time CGM **A** or intermittently scanned CGM **E** should be offered for diabetes management at diagnosis or as soon as possible in youth with diabetes on multiple daily injections or insulin pump therapy who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual's and family's circumstances, desires, and needs.

14.19 Automated insulin delivery (AID) systems should be offered for diabetes management to youth with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual's and family's circumstances, desires, and needs. **A**

14.20 Insulin pump therapy alone should be offered for diabetes management to youth on multiple daily injections with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers) if unable to use AID systems. The choice of device should be made based on the individual's and family's circumstances, desires, and needs. **A**

14.21 Students must be supported at school in the use of diabetes technology, including continuous glucose monitors, insulin pumps, connected insulin pens, and AID systems as prescribed by their diabetes care team. **E**

14.22 A1C goals must be individualized and reassessed over time. An A1C of $<$7% ($<$53 mmol/mol) is appropriate for many children and adolescents. **B**

14.23 Less stringent A1C goals (such as <7.5% [<58 mmol/mol]) may be appropriate for youth who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulins, advanced insulin delivery technology, and/or CGM; cannot check blood glucose regularly; or have nonglycemic factors that increase A1C (e.g., high glycators). **B**

14.24 Even less stringent A1C goals (such as <8% [<64 mmol/mol]) may be appropriate for individuals with a history of severe hypoglycemia, limited life expectancy, or where the harms of treatment are greater than the benefits. **B**

14.25 Health care professionals may reasonably suggest more stringent A1C goals (such as <6.5% [<48 mmol/mol]) for selected individuals if they can be achieved without significant hypoglycemia, negative impacts on well-being, or undue burden of care or in those who have nonglycemic factors that decrease A1C (e.g., lower erythrocyte life span). Lower goals may also be appropriate during the honeymoon phase. **B**

14.26 CGM metrics derived from continuous glucose monitor use over the most recent 14 days (or longer for youth with more glycemic variability), including time in range (70–180 mg/dL [3.9–10.0 mmol/L]), time below range (<70 mg/dL [<3.9 mmol/L] and <54 mg/dL [<3.0 mmol/L]), and time above range (>180 mg/dL [>10.0 mmol/L] and >250 mg/dL [>13.9 mmol/L]), are recommended to be used in conjunction with A1C whenever possible. **E**

Current standards for diabetes management reflect the need to minimize hyperglycemia as safely as possible. The Diabetes Control and Complications Trial (DCCT), which did not enroll children <13 years of age, demonstrated that near normalization of blood glucose levels was more difficult to achieve in adolescents than in adults. Nevertheless, the increased use of basal-bolus plans, insulin pumps, frequent blood glucose monitoring, CGM, AID systems, goal setting, and improved patient education has been associated with more children and adolescents reaching the blood glucose goals recommended by the ADA (77–79), particularly in families in which both the parents/caregivers and the child with diabetes participate jointly to perform the required diabetes-related tasks.

Lower A1C in adolescence and young adulthood is associated with a lower risk and rate of microvascular and macrovascular complications (80–83) and demonstrates the effects of metabolic memory (84–87).

In addition, type 1 diabetes can be associated with adverse effects on cognition during childhood and adolescence (6,88–90), and neurocognitive imaging differences related to hyperglycemia in children provide another motivation for achieving glycemic goals (6). DKA has been shown to cause adverse effects on brain development and function. Additional factors (91–94) that contribute to adverse effects on brain development and function include young age, severe hypoglycemia at <6 years of age, and chronic hyperglycemia (95,96). However, meticulous use of therapeutic modalities such as rapid- and long-acting insulin analogs, technological advances (e.g., CGM, sensor-augmented pump therapy, and AID systems), and intensive self-management education now make it more feasible to achieve glycemic goals while reducing the incidence of severe hypoglycemia (97–120). Please refer to Section 7, "Diabetes Technology," for more information on technology to support people with diabetes.

In selecting individualized glycemic goals, the long-term health benefits of achieving a lower A1C should be balanced against the risks of hypoglycemia and the developmental burdens of intensive treatment plans in youth (121). Recent data with newer devices and insulins indicate that the risk of hypoglycemia with lower A1C is less than it was before (122–131). Some data suggest that there could be a threshold where lower A1C is associated with more hypoglycemia (132,133); however, the confidence intervals were large, suggesting great variability. In addition, achieving lower A1C levels is likely facilitated by setting lower A1C goals (134,135). Lower goals may be possible during the honeymoon phase of type 1 diabetes. Special consideration should be given to the risk of hypoglycemia in young children (aged <6 years) who are often unable to recognize, articulate, and/or manage hypoglycemia. However, registry data indicate that A1C goals can be achieved in children, including those aged <6 years, without increased risk of severe hypoglycemia (123,134). Recent data have demonstrated that the use of real-time CGM lowered A1C and increased TIR in adolescents and young adults and, in children aged <8 years old, was associated with a lower risk of hypoglycemia (136,137). Please refer to Section 6, "Glycemic Goals and Hypoglycemia," for more information on glycemic assessment.

A strong relationship exists between the frequency of blood glucose monitoring and glycemic management (118–120, 138–144). Glucose levels for all children and adolescents with type 1 diabetes should be monitored multiple times daily by blood glucose monitoring and/or CGM. Recent data on children and adults suggest that use of CGM soon after type 1 diabetes diagnosis is associated with improved A1C (104,105,145). In the U.S., real-time CGM is approved for nonadjunctive use in children aged 2 years and older and intermittently scanned CGM is approved for nonadjunctive use in children aged 4 years and older. Parents/caregivers and youth should be offered initial and ongoing education and support for CGM use. Behavioral support may further improve ongoing CGM use (137). Metrics derived from CGM include percent time in target range, below target range, and above target range (146). While studies indicate a relationship between TIR and A1C (147,148), it is still uncertain what the ideal goal TIR should be for children, and further studies are needed. Please refer to Section 7, "Diabetes Technology," for more information on the use of blood glucose meters, CGM, and insulin pumps. More information on insulin injection technique can be found in Section 9, "Pharmacologic Approaches to Glycemic Treatment."

Key Concepts in Setting Glycemic Goals

- Glycemic goals should be individualized, and lower goals may be reasonable based on a benefit–risk assessment.
- Blood glucose goals should be modified in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to

assess preprandial insulin doses in those on basal-bolus or pump plans.

Autoimmune Conditions

Recommendation

14.27 Assess for additional autoimmune conditions soon after the diagnosis of type 1 diabetes and if symptoms develop. **B**

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction and celiac disease should be considered (149–153). Periodic screening in asymptomatic individuals has been recommended, but the optimal frequency of screening is unclear.

Although much less common than thyroid dysfunction and celiac disease, other autoimmune conditions, such as Addison disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis, occur more commonly in the population with type 1 diabetes than in the general pediatric population and should be assessed and monitored as clinically indicated. In addition, relatives of youth with type 1 diabetes should be offered testing for islet autoantibodies through research studies (e.g., TrialNet) and national programs for early diagnosis of preclinical type 1 diabetes (stages 1 and 2).

Thyroid Disease

Recommendations

14.28 Consider testing children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis. **B**

14.29 Measure thyroid-stimulating hormone concentrations at diagnosis when clinically stable or soon after optimizing glycemia. If normal, suggest rechecking every 1–2 years or sooner if the youth has positive thyroid antibodies or develops symptoms or signs suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unexplained glycemic variability. **B**

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of individuals with type 1 diabetes (150, 154,155). At the time of diagnosis, ~25% of children with type 1 diabetes have thyroid autoantibodies (156), the presence of which is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of people with type 1 diabetes (157,158). For thyroid autoantibodies, a study from Sweden indicated that antithyroid peroxidase antibodies were more predictive than antithyroglobulin antibodies in multivariate analysis (159). Thyroid function tests may be misleading (euthyroid sick syndrome) if performed at the time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, if performed at diagnosis and slightly abnormal, thyroid function tests should be repeated soon after a period of metabolic stability and achievement of glycemic goals. Subclinical hypothyroidism may be associated with an increased risk of symptomatic hypoglycemia (160) and a reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of glycemia.

Celiac Disease

Recommendations

14.30 Screen youth with type 1 diabetes for celiac disease by measuring IgA tissue transglutaminase (tTG) antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes, or IgG tTG and deamidated gliadin antibodies if IgA is deficient. **B**

14.31 Repeat screening for celiac disease within 2 years of diabetes diagnosis and then again after 5 years and consider more frequent screening in youth who have symptoms or a first-degree relative with celiac disease. **B**

14.32 Individuals with confirmed celiac disease should be placed on a gluten-free diet for treatment and to avoid complications. Youth and their caregivers should also have a consultation with a registered dietitian nutritionist experienced in managing both diabetes and celiac disease. **B**

Celiac disease is an immune-mediated disorder that occurs with increased frequency in people with type 1 diabetes (1.6–16.4% of individuals compared with 0.3–1% in the general population) (149, 152,153,161–165). Screening people with type 1 diabetes for celiac disease is further justified by its association with osteoporosis, iron deficiency, growth failure, and potential increased risk of retinopathy and albuminuria (166–169).

Screening for celiac disease includes measuring serum levels of IgA and tissue transglutaminase (tTG) IgA antibodies, or, with IgA deficiency, screening can include measuring tTG IgG antibodies or deamidated gliadin peptide IgG antibodies. Because most cases of celiac disease are diagnosed within the first 5 years after the diagnosis of type 1 diabetes, screening should be considered at the time of diagnosis and repeated at 2 and then 5 years (163) or if clinical symptoms indicate, such as poor growth or increased hypoglycemia (164,166).

Although celiac disease can be diagnosed more than 10 years after diabetes diagnosis, there are insufficient data after 5 years to determine the optimal screening frequency. Measurement of tTG antibody should be considered at other times in individuals with symptoms suggestive of celiac disease (163). Monitoring for symptoms should include an assessment of linear growth and weight gain (164,166). A small bowel biopsy in antibody-positive children is recommended to confirm the diagnosis (170). European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggest that biopsy may not be necessary in symptomatic children with high antibody titers (i.e., greater than 10 times the upper limit of normal) provided that further testing is performed (verification of endomysial antibody positivity on a separate blood sample) (171). Whether this approach may be appropriate for asymptomatic children in high-risk groups remains an open question, though evidence is emerging (172). It is also advisable to check for celiac disease–associated HLA types in individuals who are diagnosed without a small intestinal biopsy. In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (173). The challenging dietary restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, a biopsy to confirm the diagnosis of celiac disease is recommended, especially in asymptomatic children, before establishing a diagnosis of celiac disease (171) and endorsing significant dietary changes. A gluten-free diet was beneficial in asymptomatic adults with positive antibodies confirmed by biopsy (174).

Management of Cardiovascular Risk Factors

Hypertension Screening

Recommendation

14.33 Blood pressure should be measured at every routine visit. In youth with high blood pressure (blood pressure ≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, blood pressure ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered. **B**

Hypertension Treatment

Recommendations

14.34 Treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management. **C**

14.35 In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.36 The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg. **C**

Blood pressure measurements should be performed using the appropriate size cuff with the youth seated and relaxed. Elevated blood pressure should be confirmed on at least three separate days, and ambulatory blood pressure monitoring should be considered. Evaluation should proceed as clinically indicated (175,176). Treatment is generally initiated with an ACE inhibitor, but an angiotensin receptor blocker can be used if the ACE inhibitor is not tolerated (e.g., due to cough) (177).

Dyslipidemia Screening

Recommendations

14.37 Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved and age is ≥2 years. If initial LDL cholesterol is ≤100 mg/dL (≤2.6 mmol/L), subsequent testing should be performed at 9–11 years of age. **B** Initial testing may be done with a nonfasting lipid level with confirmatory testing with a fasting lipid panel.

14.38 If LDL cholesterol values are within the accepted risk level (<100 mg/dL [<2.6 mmol/L]), a lipid profile repeated every 3 years is reasonable. **E**

Dyslipidemia Treatment

Recommendations

14.39 If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutrition therapy to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid trans fats, and aim for ∼10% calories from monounsaturated fats. **A**

14.40 After the age of 10 years, addition of a statin may be considered in youth with type 1 diabetes who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol >160 mg/dL (>4.1 mmol/L) or LDL cholesterol >130 mg/dL (>3.4 mmol/L) and one or more cardiovascular disease risk factors. **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.41 The goal of therapy is an LDL cholesterol value <100 mg/dL (<2.6 mmol/L). **E**

Population-based studies estimate that 14–45% of children with type 1 diabetes have two or more atherosclerotic cardiovascular disease (ASCVD) risk factors (178–180), and the prevalence of cardiovascular disease (CVD) risk factors increase with age (180) and among racial/ethnic minorities (40), with girls having a higher risk burden than boys (179).

Pathophysiology. The atherosclerotic process begins in childhood, and although ASCVD events are not expected to occur during childhood, observations using a variety of methodologies show that youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis (181–183). Studies of carotid intima media thickness have yielded inconsistent results (176,177).

Screening. Diabetes predisposes to the development of accelerated arteriosclerosis. Lipid evaluation for these individuals contributes to risk assessment and identifies an important proportion of those with dyslipidemia. Therefore, initial screening should be done soon after diagnosis. If the initial screen is normal, subsequent screening may be done at 9–11 years of age, which is a stable time for lipid assessment in children (184). Children with a primary lipid disorder (e.g., familial hyperlipidemia) should be referred to a lipid specialist. Non-HDL cholesterol level has been identified as a significant predictor of the presence of atherosclerosis—as powerful as any other lipoprotein cholesterol measure in children and adolescents. For both children and adults, non-HDL cholesterol level seems to be more predictive of persistent dyslipidemia and, therefore, atherosclerosis and future events than total cholesterol, LDL cholesterol, or HDL cholesterol levels alone. A major advantage (185) of non-HDL cholesterol is that it can be accurately calculated in a nonfasting state and therefore is practical to obtain in clinical practice as a screening test (186). Youth with type 1 diabetes have a high prevalence of lipid abnormalities (178,185).

Even if normal, screening should be repeated within 3 years, as A1C and other cardiovascular risk factors can change dramatically during adolescence (187).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes and secondary dyslipidemia (176,184,188,189); however, there are few studies on modifying lipid levels in children with type 1 diabetes. A 6-month trial of dietary counseling produced a significant improvement in lipid levels (190); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (191). Data from the SEARCH for Diabetes in Youth (SEARCH) study show that improved glucose over a 2-year period is associated with a more favorable lipid profile; however, improved glycemia alone will not normalize lipids in youth with type 1 diabetes and dyslipidemia (187).

Although intervention data are sparse, the American Heart Association categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels (189,192). Initial therapy should include a nutrition plan that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day (184). Data from randomized clinical trials in children as young as 7 months of age indicate that this diet is safe and does not interfere with normal growth and development (193).

Neither long-term safety nor cardiovascular outcome efficacy of statin therapy has been established for children; however, studies have shown short-term safety equivalent to that seen in adults and efficacy in lowering LDL cholesterol levels in familial hypercholesterolemia or severe hyperlipidemia, improving endothelial function and causing regression of carotid intimal thickening (194,195). Statins are not approved for children aged <10 years, and statin treatment should generally not be used in children with type 1 diabetes before this age. Statins are contraindicated in pregnancy; therefore, the prevention of unplanned pregnancies is of paramount importance. Statins should be avoided in individuals of childbearing age who are not using reliable contraception (see Section 15, "Management of Diabetes in Pregnancy," for more information). The multicenter, randomized, placebo-controlled Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) provides safety data on pharmacologic treatment with an ACE inhibitor and statin in adolescents with type 1 diabetes (176).

Microvascular Complications

Nephropathy Screening

Recommendation

14.42 Annual screening for albuminuria with a random (morning sample preferred to avoid effects of exercise) spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the youth has had diabetes for 5 years. **B**

Nephropathy Treatment

Recommendation

14.43 An ACE inhibitor or an angiotensin receptor blocker, titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented (two of three urine samples obtained over a 6-month interval following efforts to improve glycemia and normalize blood pressure). **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

Data from 7,549 participants <20 years of age in the T1D Exchange clinic registry emphasize the importance of meeting glycemic and blood pressure goals, particularly as diabetes duration increases, in order to reduce the risk of diabetic kidney disease. The data also underscore the importance of routine screening to ensure early diagnosis and timely treatment of albuminuria (196). An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex (197), should be considered at baseline and repeated as indicated based on clinical status, age, diabetes duration, and therapies. Improved methods are needed to screen for early GFR loss since estimated GFR is inaccurate at GFR >60 mL/min/1.73 m^2 (197,198). The AdDIT study in adolescents with type 1 diabetes demonstrated the safety of ACE inhibitor treatment, but the treatment did not change the albumin-to-creatinine ratio over the course of the study (176).

Retinopathy

Recommendations

14.44 An initial dilated and comprehensive eye examination is recommended once youth have had type 1 diabetes for 3–5 years, provided they are aged ≥ 11 years or puberty has started, whichever is earlier. **B**

14.45 After the initial examination, repeat dilated and comprehensive eye examination every 2 years. Less frequent examinations, every 4 years, may be acceptable on the advice of an eye care professional and based on risk factor assessment, including a history of A1C $<8\%$. **B**

14.46 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **E**

Retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (199). It is currently recognized that there is a low risk of development of vision-threatening retinal lesions prior to 12 years of age (200,201). A 2019 publication based on the follow-up of the DCCT adolescent cohort supports a lower frequency of eye examinations than previously recommended, particularly in adolescents with A1C closer to the goal range (202,203). Referrals should be made to eye care professionals with expertise in diabetic retinopathy and experience in counseling pediatric patients and families on the importance of prevention, early detection, and intervention.

Neuropathy

Recommendation

14.47 Consider an annual comprehensive foot exam at the start of puberty or at age ≥ 10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. The examination should include inspection, assessment of foot pulses, pinprick, and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. **B**

Diabetic neuropathy rarely occurs in prepubertal children or after only 1–2 years of diabetes (199), although data suggest a prevalence of distal peripheral neuropathy of 7% in 1,734 youth with type 1 diabetes and association with the presence of CVD risk factors (204,205). A comprehensive foot exam, including inspection, palpation of dorsalis pedis and posterior tibial pulses, and determination of proprioception, vibration, and monofilament sensation, should be performed annually along with an assessment of symptoms of neuropathic pain (205). Foot inspection can be performed at each visit to educate youth regarding the importance of foot care (see Section 12, "Retinopathy, Neuropathy, and Foot Care").

TYPE 2 DIABETES

For information on risk-based screening for type 2 diabetes and prediabetes in youth, please refer to Section 2, "Diagnosis and Classification of Diabetes." For additional support for these recommendations, see the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3).

The prevalence of type 2 diabetes in youth has continued to increase over the past 20 years (4). The CDC published projections for type 2 diabetes prevalence using the SEARCH database; assuming a 2.3% annual increase, the prevalence in those under 20 years of age will quadruple in 40 years (206,207).

Evidence suggests that type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique features, such as a more rapidly progressive decline in β-cell function and accelerated development of diabetes complications (3,208). Long-term follow-up data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study showed that a majority of individuals with type 2 diabetes diagnosed as youth had microvascular complications by young adulthood (209). Type 2 diabetes disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviors (41,210–213). Additional risk factors associated with type 2 diabetes in youth include adiposity, family history of diabetes, female sex, and low socioeconomic status (208).

As with type 1 diabetes, youth with type 2 diabetes spend much of the day in school. Therefore, close communication with and the cooperation of school personnel are essential for optimal diabetes management, safety, and maximal academic opportunities.

Screening and Diagnosis

Recommendations

14.48 Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or ≥10 years of age, whichever occurs earlier, in youth with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes (see **Table 2.5** for evidence grading of other risk factors).

14.49 If screening is normal, repeat screening at a minimum of 3-year intervals, **E** or more frequently if BMI is increasing. **C**

14.50 Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents. **B**

14.51 Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes. **B**

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in racial and ethnic minority populations (184,214). A few studies suggest oral glucose tolerance tests or fasting plasma glucose values as more suitable diagnostic tests than A1C in the pediatric population, especially among certain ethnicities (215), although fasting glucose alone may overdiagnose diabetes in children (216,217). In addition, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (218). An analysis of National Health and Nutrition Examination Survey (NHANES) data suggests using A1C for screening of high-risk youth (219).

The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes, and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this population (214,215).

Diagnostic Challenges

Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Overweight and obesity are common in children with type 1 diabetes (42), and diabetes-associated autoantibodies and ketosis may be present in pediatric individuals with clinical features of type 2 diabetes (including obesity and acanthosis nigricans) (216). The presence of islet autoantibodies has been associated with faster progression to insulin deficiency (216). At the onset, DKA occurs in ∼6% of youth aged 10–19 years with type 2 diabetes (220). Although uncommon, type 2 diabetes has been observed in prepubertal children under the age of 10 years, and thus it should be part of the differential in children with suggestive symptoms (221). Finally, obesity contributes to the development of type 1 diabetes in some individuals (222), which further blurs the lines between diabetes types. However, accurate diagnosis is critical, as treatment plans, educational approaches, dietary advice, and outcomes differ markedly between individuals with the two diagnoses. The significant diagnostic difficulties posed by MODY are discussed in Section 2, "Diagnosis and Classification of Diabetes." In addition, there are rare and atypical diabetes cases that represent a challenge for clinicians and researchers.

Management

Lifestyle Management

Recommendations

14.52 All youth with type 2 diabetes and their families should receive comprehensive diabetes self-management education and support that is specific to youth with type 2 diabetes and is culturally appropriate. **B**

14.53 Youth with overweight/obesity and type 2 diabetes and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management to achieve at least a 7–10% decrease in excess weight. **C**

14.54 Given the necessity of long-term weight management for youth with type 2 diabetes, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care. **E**

14.55 Youth with prediabetes and type 2 diabetes, like all children and adolescents, should be encouraged to participate in at least 60 min of moderate to vigorous physical activity daily (with muscle and bone strength training at least 3 days/week) **B** and to decrease sedentary behavior. **C**

14.56 Nutrition for youth with prediabetes and type 2 diabetes, like for all children and adolescents, should focus on healthy eating patterns that emphasize consumption of nutrient-dense, high-quality foods and decreased consumption of calorie-dense, nutrient-poor foods, particularly sugar-added beverages. **B**

Glycemic Goals

Recommendations

14.57 Blood glucose monitoring should be individualized, taking into consideration the pharmacologic treatment of the youth with type 2 diabetes. **E**

14.58 Real-time CGM or intermittently scanned CGM should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or insulin pumps who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on an individual's and family's circumstances, desires, and needs. **E**

14.59 Glycemic status should be assessed at least every 3 months. **E**

14.60 A reasonable A1C goal for most children and adolescents with type 2 diabetes is <7% (<53 mmol/mol). More stringent A1C goals (such as <6.5% [<48 mmol/mol]) may be appropriate for selected individuals if they can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate individuals might include those with a short duration of diabetes and lesser degrees of β-cell dysfunction and individuals treated with lifestyle or metformin only who achieve significant weight improvement. **E**

14.61 Less stringent A1C goals (such as 7.5% [58 mmol/mol]) may be appropriate if there is an increased risk of hypoglycemia. **E**

14.62 A1C goals for individuals on insulin should be individualized, taking into account the relatively low rates of hypoglycemia in youth-onset type 2 diabetes. **E**

Pharmacologic Management

Recommendations

14.63 Initiate pharmacologic therapy, in addition to behavioral counseling for healthful nutrition and physical activity changes, at diagnosis of type 2 diabetes. **A**

14.64 In individuals with incidentally diagnosed or metabolically stable diabetes (A1C <8.5% [<69 mmol/mol] and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal. **A**

14.65 Youth with marked hyperglycemia (blood glucose ≥250 mg/dL [≥13.9 mmol/L], A1C ≥8.5% [≥69 mmol/mol]) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with long-acting insulin while metformin is initiated and titrated. **B**

14.66 In individuals with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued. **A**

14.67 In individuals presenting with severe hyperglycemia (blood glucose ≥600 mg/dL [≥33.3 mmol/L]), consider assessment for hyperglycemic hyperosmolar nonketotic syndrome. **A**

14.68 If glycemic goals are no longer met with metformin (with or without long-acting insulin), glucagon-like peptide 1 (GLP-1) receptor agonist therapy and/or empagliflozin should be considered in children 10 years of age or older. **A**

14.69 When choosing glucose-lowering or other medications for youth with overweight or obesity and type 2 diabetes, consider medication-taking behavior and the medications' effect on weight. **E**

14.70 For youth not meeting glycemic goals, maximize noninsulin therapies (metformin, a GLP-1 receptor agonist, and empagliflozin) before initiating and/or intensifying insulin therapy plan. **E**

14.71 In individuals initially treated with insulin and metformin and/or other glucose lowering medications who are meeting glucose goals based on blood glucose monitoring or CGM, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days. **B**

Treatment of youth-onset type 2 diabetes should include lifestyle management, diabetes self-management education and support, and pharmacologic treatment. Initial treatment of youth with obesity and diabetes must take into account that diabetes type is often uncertain in the first few weeks of treatment due to overlap in presentation and that a substantial percentage of youth with type 2 diabetes will present with clinically significant ketoacidosis (223). Therefore, initial therapy should address the hyperglycemia and associated metabolic derangements irrespective of ultimate diabetes type, with adjustment of therapy once metabolic compensation has been established and subsequent information, such as islet autoantibody results, becomes available. **Figure 14.1** provides an approach to the initial treatment of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes.

Glycemic goals should be individualized, taking into consideration the long-term health benefits of more stringent goals and risk for adverse effects, such as hypoglycemia. A lower A1C goal in youth with type 2 diabetes when compared with those recommended in type 1 diabetes is justified by a lower risk of hypoglycemia and higher risk of complications (209,224–227).

Self-management in pediatric diabetes involves both the youth and their parents/adult caregivers. Individuals and their families should receive education and support for healthful nutrition and physical activity, such as a balanced meal plan, achieving and maintaining a healthy weight, and regular physical activity. Youth with type 2

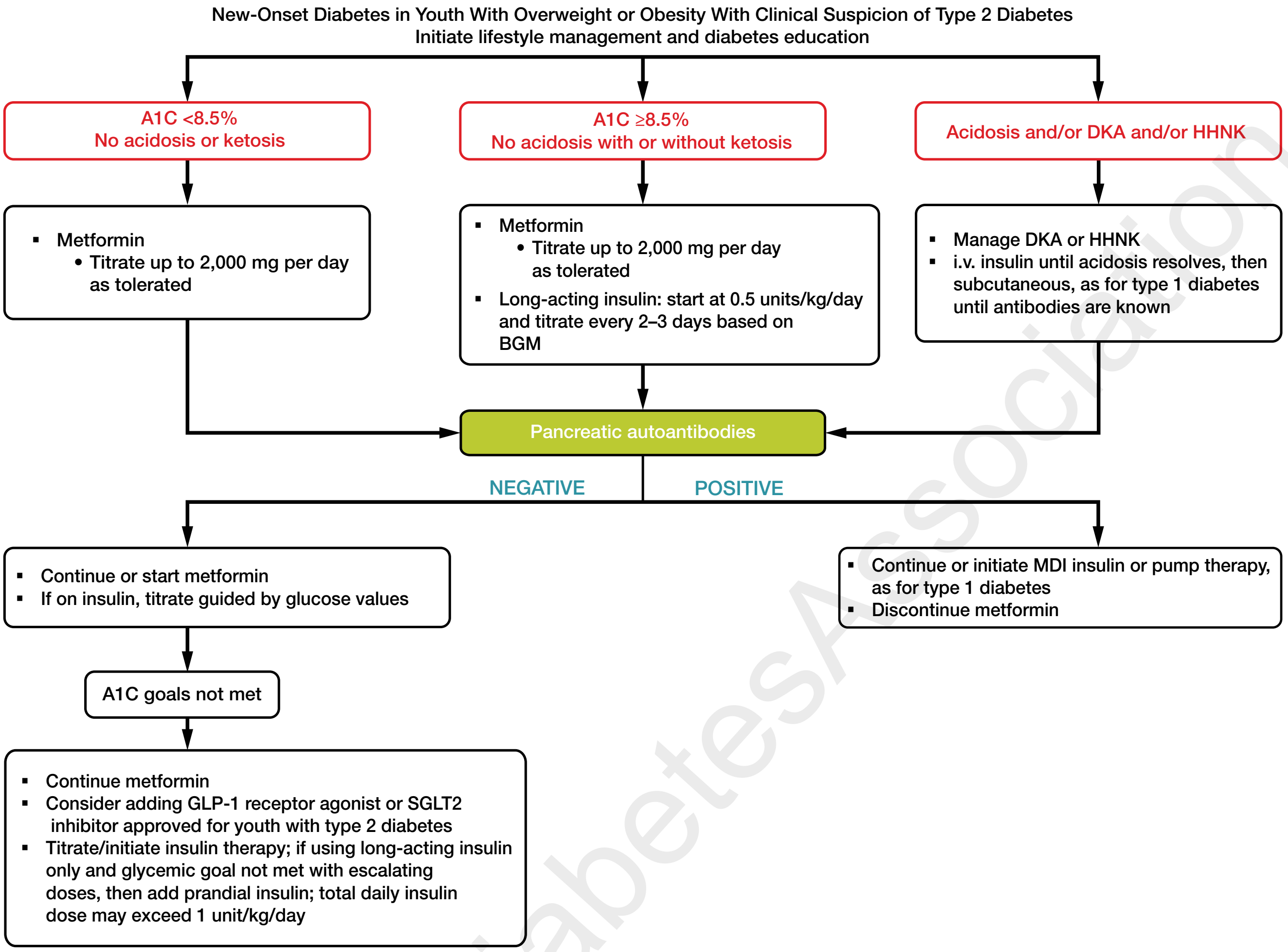
New-Onset Diabetes in Youth With Overweight or Obesity With Clinical Suspicion of Type 2 Diabetes
Initiate lifestyle management and diabetes education
A1C <8.5%
No acidosis or ketosis
A1C ≥8.5%
No acidosis with or without ketosis
Acidosis and/or DKA and/or HHNK
Metformin
Titrate up to 2,000 mg per day as tolerated
Metformin
Titrate up to 2,000 mg per day as tolerated
Long-acting insulin: start at 0.5 units/kg/day and titrate every 2–3 days based on BGM
Manage DKA or HHNK
i.v. insulin until acidosis resolves, then subcutaneous, as for type 1 diabetes until antibodies are known
Pancreatic autoantibodies
NEGATIVE
POSITIVE
Continue or start metformin
If on insulin, titrate guided by glucose values
Continue or initiate MDI insulin or pump therapy, as for type 1 diabetes
Discontinue metformin
A1C goals not met
Continue metformin
Consider adding GLP-1 receptor agonist or SGLT2 inhibitor approved for youth with type 2 diabetes
Titrate/initiate insulin therapy; if using long-acting insulin only and glycemic goal not met with escalating doses, then add prandial insulin; total daily insulin dose may exceed 1 unit/kg/day

Figure 14.1—Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes. A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement “Evaluation and Management of Youth-Onset Type 2 Diabetes” (3). BGM, blood glucose monitoring; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; GLP-1, glucagon-like peptide 1; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; i.v., intravenous; MDI, multiple daily injections; SGLT2, sodium–glucose cotransporter 2.

diabetes and comorbidities, including nephropathy, should continue to have age-appropriate protein intake (228). Physical activity should include aerobic, muscle-strengthening, and bone-strengthening activities (33). A family-centered approach to nutrition and lifestyle modification is essential in children and adolescents with type 2 diabetes, and nutrition recommendations should be culturally appropriate and sensitive to family resources (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”). Given the complex social and environmental context surrounding youth with type 2 diabetes, individual-level lifestyle interventions may not be sufficient to address the complex interplay of family dynamics, behavioral health, community readiness, and the broader environmental system (3).

An interprofessional diabetes team, including a physician, diabetes care and education specialist, registered dietitian nutritionist, and psychologist or social worker, is essential. In addition to achieving glycemic goals and self-management education (229–231), initial treatment must include management of comorbidities such as obesity, dyslipidemia, hypertension, and microvascular complications.

Current pharmacologic treatment options for youth-onset type 2 diabetes are limited to four approved drug classes: insulin, metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium–glucose cotransporter 2 inhibitors (specifically empagliflozin). Presentation with ketoacidosis or marked ketosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal or near-normal levels. Insulin pump therapy may be considered as an option for those on long-term multiple daily injections who are able to safely manage the device. Initial treatment should also be with insulin when the distinction between type 1 diabetes and type 2 diabetes is unclear and in individuals who have random blood glucose concentrations ≥250 mg/dL (≥13.9 mmol/L) and/or A1C ≥8.5% (≥69 mmol/mol) (232). Metformin therapy should be added after resolution of ketosis/ketoacidosis.

When initial insulin treatment is not required, initiation of metformin is recommended. The TODAY study found that metformin alone provided durable glycemic control (A1C ≤8% [≤64 mmol/mol] for 6 months) in approximately half of the subjects (233). The Restoring Insulin Secretion (RISE) Consortium study did not demonstrate differences in measures of glucose or β-cell function preservation between metformin and insulin, but there was more weight gain with insulin (234).

To date, the TODAY study is the only trial combining lifestyle and metformin therapy in youth with type 2 diabetes; the combination did not perform better than metformin alone in achieving durable glycemic levels (233).

Randomized controlled trials in youth have shown that GLP-1 receptor agonists are safe and effective for decreasing A1C (235–239). Use of GLP-1 receptor agonists can increase the frequency of gastrointestinal side effects and should not be used in individuals with a family history of medullary thyroid cancer.

In a recent multicenter double-blind, placebo-controlled trial, 158 children with type 2 diabetes aged between 10 and 17 years were randomized to 10 mg empagliflozin, 5 mg linagliptin, or placebo. There was a significant reduction in the primary outcome (A1C): −0.84% from baseline in the empagliflozin group compared with the placebo group ($P = 0.012$). There were no episodes of severe hypoglycemia during the study (240).

Blood glucose monitoring plans should be individualized, taking into consideration the pharmacologic treatment of the person. Although data on CGM in youth with type 2 diabetes are sparse (241), CGM could be considered in individuals requiring frequent blood glucose monitoring for diabetes management.

Metabolic Surgery

Recommendations

14.72 Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who have class 2 obesity or higher (BMI >35 kg/m^2 or 120% of 95th percentile for age and sex, whichever is lower) and who have elevated A1C and/or serious comorbidities despite lifestyle and pharmacologic intervention. **A**

14.73 Metabolic surgery should be performed only by an experienced surgeon working as part of a well-organized and engaged interprofessional team, including a surgeon, endocrinologist, registered dietitian nutritionist, behavioral health specialist, and nurse. **A**

The results of weight loss and lifestyle interventions for obesity in children and adolescents have been disappointing, and treatment options as adjuncts to lifestyle therapy are limited. Recent U.S. Food and Drug Administration–approved medications for youth ages 12 and older include phentermine and topiramate extended-release capsules and GLP-1 receptor agonists (242–245). Over the last decade, weight loss surgery has been increasingly performed in adolescents with obesity. Small retrospective analyses and a prospective multicenter, nonrandomized study suggest that bariatric or metabolic surgery have benefits in adolescents with obesity and type 2 diabetes similar to those observed in adults. Teenagers experience similar degrees of weight loss, diabetes remission, and improvement of cardiometabolic risk factors for at least 3 years after surgery (246). A secondary data analysis from the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and TODAY studies suggests surgical treatment of adolescents with severe obesity and type 2 diabetes is associated with improved glycemia (247); however, no randomized trials have yet compared the effectiveness and safety of surgery to those of conventional treatment options in adolescents (248). The guidelines used as an indication for metabolic surgery in adolescents generally include class 2 obesity or higher (BMI >35 kg/m^2 or 120% of 95th percentile for age and sex, whichever is lower, with comorbidities) or BMI >40 kg/m^2 with or without comorbidities (249–261). A number of groups, including the Pediatric Bariatric Study Group and Teen-LABS study, have demonstrated the effectiveness of metabolic surgery in adolescents (253–259).

Prevention and Management of Diabetes Complications

Hypertension

Recommendations

14.74 Blood pressure should be measured at every clinic visit. In youth with high blood pressure (blood pressure ≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered. **B**

14.75 Treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management. **C**

14.76 In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.77 The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg. **C**

Nephropathy

Recommendations

14.78 Protein intake should be at the recommended daily allowance of 0.85–1.2 g/kg/day (according to age). **E**

14.79 Urine albumin-to-creatinine ratio should be obtained at the time of diagnosis and annually thereafter. An elevated urine albumin-to-creatinine ratio (>30 mg/g creatinine) should be confirmed on two of three samples. **B**

14.80 Estimated glomerular filtration rate (GFR) should be determined at the time of diagnosis and annually thereafter. **E**

14.81 In youth with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and is strongly recommended for those with urinary albumin-to-creatinine ratio >300 mg/g creatinine and/or estimated GFR <60 mL/min/1.73 m^2. **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.82 For youth with nephropathy, continue monitoring (yearly and/or as indicated by urinary albumin-to-creatinine ratio and estimated GFR) to detect disease progression. **E**

14.83 Referral to nephrology is recommended in case of uncertainty of etiology, worsening urinary albumin-to-creatinine ratio, or decrease in estimated GFR. **E**

Neuropathy

Recommendations

14.84 Youth with type 2 diabetes should be screened for the presence of neuropathy by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. **C**

14.85 Prevention of neuropathy should focus on achieving glycemic goals. **C**

Retinopathy

Recommendations

14.86 Screening for retinopathy should be performed by dilated fundoscopy at or soon after diagnosis and annually thereafter. **C**

14.87 Optimizing glycemia is recommended to decrease the risk or slow the progression of retinopathy. **B**

14.88 Less frequent examination (every 2 years) may be considered if achieving glycemic goals and a normal eye exam. **C**

14.89 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **E**

Nonalcoholic Fatty Liver Disease

Recommendations

14.90 Evaluation of youth with type 2 diabetes for nonalcoholic fatty liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter. **B**

14.91 Referral to gastroenterology should be considered for persistently elevated or worsening transaminases. **B**

Obstructive Sleep Apnea

Recommendation

14.92 Screening for symptoms of sleep apnea should be done at each visit, and referral to a pediatric sleep specialist for evaluation and a polysomnogram, if indicated, is recommended. Obstructive sleep apnea should be treated when documented. **B**

Polycystic Ovary Syndrome

Recommendations

14.93 Evaluate for polycystic ovary syndrome in female adolescents with type 2 diabetes, including laboratory studies, when indicated. **B**

14.94 Metformin, in addition to lifestyle modification, is likely to improve the menstrual cyclicity and hyperandrogenism in female individuals with type 2 diabetes. **E**

Cardiovascular Disease

Recommendation

14.95 Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood. **E**

Dyslipidemia

Recommendations

14.96 Lipid screening should be performed initially after optimizing glycemia and annually thereafter. **B**

14.97 Optimal goals are LDL cholesterol $<$100 mg/dL ($<$2.6 mmol/L), HDL cholesterol $>$35 mg/dL ($>$0.91 mmol/L), and triglycerides $<$150 mg/dL ($<$1.7 mmol/L). **E**

14.98 If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutritional therapy to limit the amount of calories from fat to 25–30% and saturated fat to $<$7%, limit cholesterol to $<$200 mg/day, avoid trans fats, and aim for $\sim$10% calories from monounsaturated fats for elevated LDL. For elevated triglycerides, medical nutrition therapy should also focus on decreasing simple sugar intake and increasing dietary n-3 fatty acids in addition to the above changes. **A**

14.99 If LDL cholesterol remains $>$130 mg/dL ($>$3.4 mmol/L) after 6 months of dietary intervention, initiate therapy with statin, with a goal of LDL $<$100 mg/dL ($<$2.6 mmol/L). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.100 If triglycerides are $>$400 mg/dL ($>$4.7 mmol/L) fasting or $>$1,000 mg/dL ($>$11.6 mmol/L) nonfasting, optimize glycemia and begin fibrate, with a goal of $<$400 mg/dL ($<$4.7 mmol/L) fasting to reduce risk for pancreatitis. **C**

Cardiac Function Testing

Recommendation

14.101 Routine screening for heart disease with electrocardiogram, echocardiogram, or stress testing is not recommended in asymptomatic youth with type 2 diabetes. **B**

Comorbidities may already be present at the time of diagnosis of type 2 diabetes in youth (208,262). Therefore, blood pressure measurement, a fasting lipid panel, assessment of random urine albumin-to-creatinine ratio, and a dilated eye examination should be performed at diagnosis. Additional medical conditions that may need to be addressed include polycystic ovary disease and other comorbidities associated with pediatric obesity, such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in children and adolescents.

Youth-onset type 2 diabetes is associated with significant microvascular and macrovascular risk burden and a substantial increase in the risk of cardiovascular morbidity and mortality at an earlier age than in those diagnosed later in life (209,263). The higher complication risk in earlier-onset type 2 diabetes is likely related to prolonged lifetime exposure to hyperglycemia and other atherogenic risk factors, including insulin resistance, dyslipidemia, hypertension, and chronic inflammation. There is a low risk of hypoglycemia in youth with type 2 diabetes, even if they are being treated with insulin (264), and there are high rates of complications (224–227). These diabetes comorbidities also appear to be higher than in youth with type 1 diabetes despite shorter diabetes duration and lower A1C (262). In addition, the progression of vascular abnormalities appears to be more pronounced in youth-onset type 2 diabetes than with type 1 diabetes of similar duration, including ischemic heart disease and stroke (263).

In youth with type 2 diabetes and polycystic ovary syndrome, oral contraceptives are appropriate agents.

Psychosocial Factors

Recommendations

14.102 Health care professionals should screen for food insecurity, housing instability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. **E**

14.103 Use age-appropriate standardized and validated tools to screen for diabetes distress, depressive symptoms, and behavioral health in youth with type 2 diabetes, with attention to symptoms of depression and disordered eating, and refer to a qualified behavioral health professional when indicated. **B**

14.104 Starting at puberty, preconception counseling should be incorporated into routine diabetes clinic visits for all individuals of childbearing potential because of the adverse pregnancy outcomes in this population. **A**

14.105 Adolescents and young adults should be screened for tobacco/nicotine, electronic cigarettes, substance use, and alcohol use at diagnosis and regularly thereafter. **C**

Most youth with type 2 diabetes come from racial/ethnic minority groups, have low socioeconomic status, and often experience multiple psychosocial stressors (41,56,212,213). Consideration of the sociocultural context and efforts to personalize diabetes management are of critical importance to minimize barriers to care, enhance participation, and maximize response to treatment.

Evidence about psychiatric disorders and symptoms in youth with type 2 diabetes is limited (265–269), but given the sociocultural context for many youth and the medical burden and obesity associated with type 2 diabetes, ongoing surveillance of behavioral health is indicated. Symptoms of depression and disordered eating are common and associated with higher A1C (53,266,270,271). Early detection of psychological and behavioral concerns can facilitate effective treatment options to improve psychosocial well-being and support diabetes (56). When psychological symptoms are identified, referral to a behavioral health professional, ideally with experience in pediatric diabetes, may be warranted. Although far less research has been done on psychological and behavioral interventions for youth with type 2 diabetes than for youth with type 1 diabetes, behavioral professionals can provide behavioral health care services to support youth with type 2 diabetes (61–63). Many of the medications prescribed for diabetes and psychiatric disorders are associated with weight gain and can increase concerns about eating, body shape, and weight (272,273).

The TODAY study documented high rates of maternal complications during pregnancy and low rates of preconception counseling and contraception use (274). Preconception counseling tailored for adolescents with diabetes (including type 2 diabetes) has sustained behavioral benefits (71).

SUBSTANCE USE IN PEDIATRIC DIABETES

Tobacco and Electronic Cigarettes

Recommendations

14.106 Elicit a smoking history at initial and follow-up diabetes visits; discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke. **A**

14.107 Electronic cigarette use should be discouraged. **A**

The adverse health effects of smoking and use of tobacco products are well recognized with respect to future cancer and CVD risk. Despite this, smoking rates are significantly higher among youth with diabetes than among youth without diabetes (275,276). In youth with diabetes, it is important to avoid additional CVD risk factors. Smoking increases the risk of the onset of albuminuria; therefore, smoking avoidance is important to prevent both microvascular and macrovascular complications (184,277). Discouraging use of tobacco products, including electronic cigarettes (278,279), is an important part of routine diabetes care. Individuals with diabetes should be advised to avoid vaping and using electronic cigarettes, either as a way to stop smoking tobacco or as a recreational drug. In younger children, it is important to assess exposure to cigarette smoke in the home because of the adverse effects of secondhand smoke and to discourage youth from ever smoking. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more information about smoking, tobacco, and electronic cigarettes in people with diabetes.

As alcohol use has implications for glycemic management and safety in youth and young adults with diabetes, efforts are warranted to reduce alcohol use and increase education about the risks of alcohol use and strategies to minimize risks. A psychoeducational intervention for adolescents with chronic medical conditions, including type 1 diabetes, has demonstrated benefits for knowledge, perceived benefits, and reduced use (280).

TRANSITION FROM PEDIATRIC TO ADULT CARE

Recommendations

14.108 Pediatric diabetes care teams should implement transition preparation programs for youth beginning in early adolescence and, at the latest, at least 1 year before the anticipated transfer from pediatric to adult health care. **E**

14.109 Interprofessional adult and pediatric health care teams should provide support and resources for adolescents, young adults, and their families prior to and during the transition process from pediatric to adult health care. **E**

14.110 Pediatric diabetes specialists should partner with youth with diabetes and their caregivers to decide on the timing of transfer to an adult diabetes specialist. **E**

Care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with type 1 or type 2 diabetes throughout childhood and adolescence. The shift from pediatric to adult health care professionals, however, often occurs abruptly as the older teen enters the next developmental stage, referred to as emerging adulthood

(281), which is a critical period for young people who have diabetes. During this period of major life transitions, youth may begin to move out of their parents' or caregivers' homes and become increasingly responsible for their diabetes care. Their new responsibilities include self-management of their diabetes, making medical appointments, and financing health care once they are no longer covered by their parents' health insurance plans (ongoing coverage until age 26 years is currently available under provisions of the U.S. Affordable Care Act). In addition to lapses in health care, this is also a period associated with deterioration in glycemic stability; increased occurrence of acute complications; psychosocial, emotional, and behavioral challenges; and the emergence of chronic complications (282–287). The transfer period from pediatric to adult care is prone to fragmentation in health care delivery, which may adversely impact health care quality, cost, and outcomes (288). Worsening diabetes health outcomes during the transition to adult care and early adulthood have been documented (289,290).

It is clear that comprehensive and coordinated planning that begins in early adolescence is necessary to facilitate a seamless transition from pediatric to adult health care (282,283,291,292). Research on effective interventions to promote successful transition to adult care is limited, although there are promising developments that may improve attendance at follow-up appointments and lower hospitalizations (293). Use of transition coordinators, technology to support communication with young adults, and other interventions may be useful in addressing the identified needs and preferences of young adults for transition (294) and in supporting successful establishment in adult care settings (295–300). Given the behavioral, psychosocial, and developmental factors that relate to this transition, diabetes care teams addressing transition should include physicians, certified diabetes care and education specialists, nurses, behavioral health professionals, nutritionists, and social workers (61,301). Resources to enhance social/peer support during the transition process may also be valuable (302). A comprehensive discussion regarding the challenges faced during this period, including specific recommendations, is found in the ADA position statement "Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems" (283).

The Endocrine Society, in collaboration with the ADA and other organizations, has developed transition tools for clinicians and youth and families (292).

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15. Management of Diabetes in Pregnancy: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. in parallel with the worldwide epidemic of obesity. Not only is the prevalence of type 1 diabetes and type 2 diabetes increasing in individuals of reproductive age, but there is also a dramatic increase in the reported rates of gestational diabetes mellitus (GDM). Diabetes confers significantly greater maternal and fetal risk largely related to the degree of hyperglycemia but also related to chronic complications and comorbidities of diabetes. In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, neonatal hyperbilirubinemia, and neonatal respiratory distress syndrome, among others. In addition, diabetes in pregnancy increases the risks of obesity, hypertension, and type 2 diabetes in offspring later in life (1,2).

Preconception Counseling

Recommendations

15.1 Starting at puberty and continuing in all people with diabetes and childbearing potential, preconception counseling should be incorporated into routine diabetes care. **A**

15.2 Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until an individual's treatment plan and A1C are optimized for pregnancy. **A**

15.3 Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C $<6.5\%$ (<48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. **A**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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All individuals with diabetes and childbearing potential should be informed about the importance of achieving and maintaining as near euglycemia as safely possible prior to conception and throughout pregnancy. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, renal anomalies, and caudal regression, directly proportional to elevations in A1C during the first 10 weeks of pregnancy (3). Although observational studies are confounded by the association between elevated periconceptional A1C and other engagement in self-care behaviors, the quantity and consistency of data are convincing and support the recommendation to optimize glycemia prior to conception with an A1C $<6.5\%$ (<48 mmol/mol), as this is associated with the lowest risk of congenital anomalies (given that organogenesis occurs primarily at 5–8 weeks of gestation), preeclampsia, and preterm birth (3–7). In a systematic review and meta-analysis of observational studies, preconception care for pregnant individuals with preexisting diabetes was associated with lower A1C and reduced risks of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age births, and neonatal intensive care unit admissions (8).

There are opportunities at any health care visit to educate all adults and adolescents with diabetes and childbearing potential about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning (9). Education and counseling should be offered, even when individuals already use contraception or do not intend to conceive. Effective preconception counseling could avert substantial health and associated cost (10) burdens in the offspring (11). Family planning should be discussed, including the benefits of long-acting, reversible contraception, and effective contraception should be prescribed and used until the individual is prepared and ready to become pregnant (12–16).

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all adults and adolescents with diabetes of childbearing potential should receive education about *1*) the risks of malformations associated with unplanned pregnancies and even with mild hyperglycemia and *2*) the use of effective contraception at all times when trying to prevent a pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions (9). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (17).

Preconception Care

Recommendations

15.4 Individuals with preexisting diabetes who are planning a pregnancy should ideally begin receiving interprofessional care for preconception, which includes an endocrinology health care professional, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available. **B**

15.5 In addition to focused attention on achieving glycemic targets, **A** standard preconception care should be augmented with extra focus on nutrition, physical activity, diabetes self-care education, and screening for diabetes comorbidities and complications. **B**

15.6 Individuals with preexisting type 1 or type 2 diabetes who are planning a pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur ideally before pregnancy or in the first trimester, and then pregnant individuals should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care health care professional. **B**

The importance of preconception care for all pregnant people is highlighted by American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 762, "Prepregnancy Counseling" (10). Preconception counseling for pregnant people with preexisting type 1 or type 2 diabetes is highly effective in reducing the risk of congenital malformations and decreasing the risk of preterm delivery and admission to neonatal intensive care units. Preconception counseling is also associated with reductions in perinatal mortality and small-for-gestational-age birth weight (18). A key point is the need to incorporate a question about plans for pregnancy into the routine primary and gynecologic care of people with diabetes. Preconception care for people with diabetes should include the standard screening and care recommended for any person planning pregnancy (10). Prescription of prenatal vitamins with at least 400 μg of folic acid (10) and 150 mg of potassium iodide (19) is recommended prior to conception. Review and counseling on the abstinence of use of nicotine products, alcohol, and recreational drugs, including marijuana, is important. Standard care includes screening for sexually transmitted diseases and thyroid disease, recommended vaccinations, routine genetic screening, a careful review of all prescription and nonprescription medications, herbal supplements, and nonherbal supplements used, and a review of travel history and plans with special attention to areas known to have Zika virus, as outlined by ACOG. See **Table 15.1** for additional details on elements of preconception care (10,20).

Counseling on the specific risks of obesity in pregnancy and lifestyle interventions to prevent and treat obesity, including referral to a registered dietitian nutritionist (RDN), is recommended (21).

Diabetes-specific counseling should include an explanation of the risks to mother and fetus related to pregnancies associated with diabetes and the ways to reduce risks, including glycemic goal setting, lifestyle and behavioral management, and medical nutrition therapy (18). The most important diabetes-specific component of preconception care is the attainment of glycemic goals prior to conception. In addition, the presence of microvascular complications is associated with higher risk of disease progression and adverse pregnancy outcomes (22). Diabetes-specific testing should include A1C, creatinine, and urinary albumin-to-creatinine ratio. Special attention should be paid to the review of the medication list for potentially harmful drugs, i.e., ACE inhibitors (23,24), angiotensin receptor blockers (23), and statins (24,25). A referral for a comprehensive eye exam is recommended. Individuals with preexisting diabetic retinopathy will need close monitoring during pregnancy to assess stability or progression of retinopathy and provide treatment if indicated (26).

GLYCEMIC GOALS IN PREGNANCY

Recommendations

15.7 Fasting, preprandial, and postprandial blood glucose monitoring are recommended in individuals with diabetes in pregnancy to achieve optimal glucose levels. Glucose goals are fasting plasma glucose <95 mg/dL (<5.3 mmol/L) and either 1-h postprandial glucose <140 mg/dL (<7.8 mmol/L) or 2-h postprandial glucose <120 mg/dL (<6.7 mmol/L). **B**

15.8 Due to increased red blood cell turnover, A1C is slightly lower during pregnancy in people with and without diabetes. Ideally, the A1C goal in pregnancy is <6% (<42 mmol/mol) if this can be achieved without significant hypoglycemia, but the goal may be relaxed to <7% (<53 mmol/mol) if necessary to prevent hypoglycemia. **B**

15.9 When used in addition to pre- and postprandial blood glucose monitoring, continuous glucose monitoring (CGM) can help to achieve the A1C goal in diabetes and pregnancy. **B**

15.10 CGM is recommended in pregnancies associated with type 1 diabetes. **A** When used in addition to blood glucose monitoring, achieving traditional pre- and postprandial goals, real-time CGM can reduce the risk for large-for-gestational age infants and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. **A**

15.11 CGM metrics may be used in addition to but should not be used as a substitute for blood glucose monitoring to achieve optimal pre- and postprandial glycemic goals. **E**

15.12 Commonly used estimated A1C and glucose management indicator calculations should not be used in pregnancy as estimates of A1C. **C**

15.13 Nutrition counseling should endorse a balance of macronutrients including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish in the eating pattern. **E**

Table 15.1—Checklist for preconception care for people with diabetes

Preconception education should include:

☐ Comprehensive nutrition assessment and recommendations for:
- Overweight/obesity or underweight
- Meal planning
- Correction of dietary nutritional deficiencies
- Caffeine intake
- Safe food preparation technique

☐ Lifestyle recommendations for:
- Regular moderate exercise
- Avoidance of hyperthermia (hot tubs)
- Adequate sleep

☐ Comprehensive diabetes self-management education
☐ Counseling on diabetes in pregnancy per current standards, including: natural history of insulin resistance in pregnancy and postpartum; preconception glycemic goals; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in people with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, still birth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.
☐ Supplementation
- Folic acid supplement (400 μg routine)
- Appropriate use of over-the-counter medications and supplements

Health assessment and plan should include:

☐ General evaluation of overall health
☐ Evaluation of diabetes and its comorbidities and complications, including DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy
☐ Evaluation of obstetric/gynecologic history, including a history of cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)
☐ Review of current medications and appropriateness during pregnancy

Screening should include:

☐ Diabetes complications and comorbidities, including comprehensive foot exam; comprehensive ophthalmologic exam; ECG in individuals starting at age 35 years who have cardiac signs/symptoms or risk factors and, if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine albumin-to-creatinine ratio
☐ Anemia
☐ Genetic carrier status (based on history):
- Cystic fibrosis
- Sickle cell anemia
- Tay-Sachs disease
- Thalassemia
- Others if indicated

☐ Infectious disease
- *Neisseria gonorrhoeae/Chlamydia trachomatis*
- Hepatitis B and hepatitis C
- HIV
- Pap smear
- Syphilis

Immunizations should include:

☐ Inactivated influenza
☐ Tdap (tetanus, diphtheria, and pertussis)
☐ COVID-19 (certain populations)
☐ Hepatitis A and hepatitis B (certain populations)
☐ Others if indicated

Preconception plan should include:

☐ Nutrition and medication plan to achieve glycemic goals prior to conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology
☐ Contraceptive plan to prevent pregnancy until glycemic goals are achieved
☐ Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

Created using information from American College of Obstetricians and Gynecologists (10) and Ramos (20). COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; DVT/PE, deep vein thrombosis/pulmonary embolism; ECG, electrocardiogram; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.

Pregnancy in people with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental factors. In people with preexisting diabetes, glycemic goals are usually achieved through a combination of insulin administration and medical nutrition therapy. Because glycemic goals in pregnancy are stricter than in nonpregnant individuals, it is important that pregnant people with diabetes eat consistent amounts of carbohydrates to match with insulin dosage and to avoid hyperglycemia or hypoglycemia. Referral to an RDN is important to establish a food plan and insulin-to-carbohydrate ratio and determine weight gain goals. The quality of the carbohydrates should be evaluated. A subgroup analysis of the Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes Trial (CONCEPTT) study demonstrated that the diets of individuals planning pregnancy and currently pregnant assessed during the run-in phase prior to randomization were characterized by high-fat, low-fiber, and poor-quality carbohydrate intakes. Fruit and vegetable consumption was inadequate, with one in four participants at risk for micronutrient deficiencies, highlighting the importance of medical nutrition therapy (27). An expert panel on nutrition in pregnancy recommends a balance of macronutrients. A diet that severely restricts any macronutrient class should be avoided, specifically the ketogenic diet that lacks carbohydrates, the Paleo diet because of dairy restriction, and any diet characterized by excess saturated fats. Nutrient-dense, whole foods are recommended, including fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish, which are less likely to promote excessive weight gain. Processed foods, fatty red meat, and sweetened foods and beverages should be limited (28).

Insulin Physiology

Given that early pregnancy may be a time of enhanced insulin sensitivity and lower glucose levels, many people with type 1 diabetes will have lower insulin requirements and an increased risk for hypoglycemia (29). At around 16 weeks, insulin resistance begins to increase, and total daily insulin doses increase linearly ∼5% per week through week 36. This usually results in a doubling of daily insulin dose compared with the prepregnancy requirement. While there is an increase in both basal and bolus insulin requirements, bolus insulin requirements take up a larger proportion of overall total daily insulin needs in individuals with preexisting diabetes as pregnancy progresses (30,31). The insulin requirement levels off toward the end of the third trimester. A rapid reduction in insulin requirements can indicate the development of placental insufficiency (32). In people with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in people with diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, fasting and postprandial blood glucose monitoring is recommended to achieve metabolic control in pregnant people with diabetes. Preprandial testing is also recommended when using insulin pumps or basal-bolus therapy so that premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic outcomes and a lower risk of preeclampsia (32–34). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic goals for preexisting diabetes in pregnancy.

Similar to the targets recommended by ACOG (upper limits are the same as for GDM, described below) (35), the ADA-recommended targets for pregnant people with type 1 or type 2 diabetes are as follows:

- Fasting glucose 70–95 mg/dL (3.9–5.3 mmol/L) and either
- One-hour postprandial glucose 110–140 mg/dL (6.1–7.8 mmol/L) or
- Two-hour postprandial glucose 100–120 mg/dL (5.6–6.7 mmol/L)

Lower limits are based on the mean of normal blood glucose in pregnancy (36). Lower limits do not apply to individuals with type 2 diabetes treated with nutrition alone. Hypoglycemia in pregnancy is as defined and treated in Recommendations 6.11–6.17 (see Section 6, “Glycemic Goals and Hypoglycemia”). The most appropriate hypoglycemia threshold level in pregnancy has not been validated but has ranged from <60 to <70 mg/dL (<3.3 to <3.9 mmol/L) in the past. Current recommendations for hypoglycemia thresholds include blood glucose <70 mg/dL (<3.9 mmol/L) and sensor glucose <63 mg/dL (<3.5 mmol/L) (36,37). These fasting/premeal and postprandial glucose values represent optimal levels if they can be achieved safely. In practice, it may be challenging for a person with type 1 diabetes to achieve these goals without hypoglycemia, particularly those with a history of recurrent hypoglycemia or hypoglycemia unawareness. If an individual cannot achieve these goals without significant hypoglycemia, the ADA suggests less stringent goals based on clinical experience and individualization of care.

A1C in Pregnancy

In studies of individuals without preexisting diabetes, increasing A1C levels within the normal range are associated with adverse outcomes (38). In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (39). Observational studies in preexisting diabetes and pregnancy show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (<42–48 mmol/mol) early in gestation (4–6,40). Clinical trials have not evaluated the risks and benefits of achieving these goals, and treatment goals should account for the risk of maternal hypoglycemia in setting an individualized goal of <6% (<42 mmol/mol) to <7% (<53 mmol/mol). Due to physiological increases in red blood cell turnover, A1C levels fall during normal pregnancy (41,42). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, although A1C may be useful, it should be used as a secondary measure of glycemic outcomes in pregnancy, after blood glucose monitoring.

In the second and third trimesters, A1C <6% (<42 mmol/mol) has the lowest risk of large-for-gestational-age infants (40,43,44), preterm delivery (45), and preeclampsia (1,46). Taking all of this into account, a goal of $<6\%$ (<42 mmol/mol) is optimal during pregnancy if it can be achieved without significant hypoglycemia. The A1C goal in a given individual should be achieved without hypoglycemia, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight (47,48). Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

Continuous Glucose Monitoring in Pregnancy

CONCEPTT was a randomized controlled trial (RCT) of real-time continuous glucose monitoring (CGM) in addition to standard care, including optimization of pre- and postprandial glucose goals versus standard care for pregnant people with type 1 diabetes. It demonstrated the value of real-time CGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C and a significant improvement in the maternal glucose time in range (TIR), without an increase in hypoglycemia, and reductions in large-for-gestational-age births, length of infant hospital stays, and severe neonatal hypoglycemia (49). An observational cohort study that evaluated the glycemic variables reported using CGM systems found that lower mean glucose, lower standard deviation, and a higher percentage of time in range were associated with lower risks of large-for-gestational-age births and other adverse neonatal outcomes (50). Data from one study suggest that the use of the CGM-reported mean glucose is superior to the use of estimated A1C, glucose management indicator, and other calculations to estimate A1C, given the changes to A1C that occur in pregnancy (51). CGM TIR can be used for assessment of glycemic outcomes in people with type 1 diabetes, but it does not provide actionable data to address fasting and postprandial hypoglycemia or hyperglycemia. The cost of CGM in pregnancies complicated by type 1 diabetes is offset by improved maternal and neonatal outcomes (52).

There are insufficient data to support the use of CGM in all people with type 2 diabetes or GDM (53,54). The decision of whether to use CGM in pregnant individuals with type 2 diabetes or GDM should be individualized based on treatment regimen, circumstances, preferences, and needs.

The international consensus on TIR (37) endorses pregnancy target ranges and goals for TIR for people with type 1 diabetes using CGM as reported on the ambulatory glucose profile; however, it does not specify the type or accuracy of the device or need for alarms and alerts. A prospective, observational study including 20 pregnant people with type 1 diabetes simultaneously monitored with intermittently scanning CGM (isCGM) and real-time CGM (rtCGM) for 7 days in early pregnancy demonstrated a higher percentage of time-below-range in the isCGM group. Asymptomatic hypoglycemia measured by isCGM should therefore not necessarily lead to a reduction of insulin dose and/or increased carbohydrate intake at bedtime unless these episodes are confirmed by blood glucose meter measurements (55). Selection of CGM device should be based on an individual's circumstances, preferences, and needs.

- Target sensor glucose range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal $>70\%$
- Time below range (<63 mg/dL [<3.5 mmol/L]): level 1 TBR, goal $<4\%$
- Time below range (<54 mg/dL [<3.0 mmol/L]): level 2 TBR, goal $<1\%$
- Time above range (>140 mg/dL [>7.8 mmol/L]): TAR, goal $<25\%$

The international consensus on TIR (37) endorsed the same sensor glucose target ranges for individuals with type 2 diabetes in pregnancy and GDM but could not quantify the goal of amount of time spent within each category because of insufficient data.

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

Recommendations

15.14 Lifestyle behavior change is an essential component of management of gestational diabetes mellitus (GDM) and may suffice as treatment for many individuals. Insulin should be added if needed to achieve glycemic goals. **A**

15.15 Insulin is the preferred medication for treating hyperglycemia in GDM. Metformin and glyburide, individually or in combination, should not be used as first-line agents, as both cross the placenta to the fetus. **A** Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data. **E**

15.16 Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. **A**

15.17 Telehealth visits used in combination with in-person visits for pregnant people with GDM can improve outcomes compared with standard in-person care alone. **A**

GDM is characterized by an increased risk of large-for-gestational-age birth weight and neonatal and pregnancy complications and an increased risk of long-term maternal type 2 diabetes and abnormal glucose metabolism of offspring in childhood. These associations with maternal oral glucose tolerance test (OGTT) results are continuous with no clear inflection points (39,56). Offspring with exposure to untreated GDM have reduced insulin sensitivity and β-cell compensation and are more likely to have impaired glucose tolerance in childhood (57). In other words, short-term and long-term risks increase with progressive maternal hyperglycemia. Therefore, all pregnant people should be screened as outlined in Section 2, "Diagnosis and Classification of Diabetes." Although there is some heterogeneity, many RCTs and a Cochrane review suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling, particularly when interventions are started during the first or early in the second trimester (58–60). There are no intervention trials in offspring of mothers with GDM. A meta-analysis of 11 RCTs demonstrated that metformin treatment in pregnancy does not reduce the risk of GDM in high-risk individuals with obesity, polycystic ovary syndrome, or preexisting insulin resistance (61). A meta-analysis of 32 RCTs evaluating the effectiveness of telemedicine interventions, which ranged from telemedicine visits to the use of health apps, used in combination with in-person visits for GDM demonstrated reduced incidences of cesarean delivery, premature rupture of membranes, pregnancy-induced hypertension or preeclampsia, preterm birth, neonatal asphyxia, and polyhydramnios compared with standard in-person care alone (62).

Lifestyle and Behavioral Management

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management, depending on pregestational weight, as outlined in the section below on preexisting type 2 diabetes, as well as glucose monitoring aiming for the goals recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (63):

- Fasting glucose <95 mg/dL (<5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (<7.8 mmol/L) or
- Two-hour postprandial glucose <120 mg/dL (<6.7 mmol/L)

The glycemic goal lower limits defined above for preexisting diabetes apply for GDM treated with insulin. Depending on the population, studies suggest that 70–85% of people diagnosed with GDM under Carpenter-Coustan criteria can manage GDM with lifestyle modification alone; it is anticipated that this proportion will be even higher if the lower International Association of the Diabetes and Pregnancy Study Groups (64) diagnostic thresholds are used.

Medical Nutrition Therapy

Medical nutrition therapy for GDM is an individualized nutrition plan developed between the pregnant person and an RDN familiar with the management of GDM (65,66). The food plan should provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote appropriate weight gain, according to the 2009 National Academy of Medicine recommendations (67). There is no definitive research that identifies a specific optimal calorie intake for people with GDM or suggests that their calorie needs are different from those of pregnant individuals without GDM. The food plan should be based on a nutrition assessment with dietary reference intake guidance from the National Academy of Medicine. The recommended dietary reference intake for all pregnant people is a minimum of 175 g of carbohydrate (∼35% of a 2,000-calorie diet), a minimum of 71 g of protein, and 28 g of fiber (68). The nutrition plan should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding *trans* fats. As is true for all nutrition therapy in people with diabetes, the amount and type of carbohydrate will impact glucose levels. Promoting higher-quality, nutrient-dense carbohydrates results in controlled fasting/postprandial glucose, lower free fatty acids, improved insulin action, and vascular benefits and may reduce excess infant adiposity. Individuals who substitute fat for carbohydrates may unintentionally enhance lipolysis, promote elevated free fatty acids, and worsen maternal insulin resistance (69,70). Fasting urine ketone testing may be useful to identify those who are severely restricting carbohydrates to manage blood glucose. Simple carbohydrates will result in higher postmeal excursions.

Physical Activity

A systematic review demonstrated improvements in glucose outcomes and reductions in need to start insulin or insulin dose requirements with an exercise intervention. There was heterogeneity in the types of effective exercise (aerobic, resistance, or both) and duration of exercise (20–50 min/day, 2–7 days/week of moderate intensity) (71).

Pharmacologic Therapy

Treatment of GDM with lifestyle and insulin has been demonstrated to improve perinatal outcomes in two large randomized studies, as summarized in a U.S. Preventive Services Task Force review (72). Insulin is the first-line agent recommended for the treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin (73,74) and glyburide (75) in reducing glucose levels for the treatment of GDM, these agents are not recommended as the first-line treatment for GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern (35). Furthermore, in separate RCTs, glyburide and metformin failed to provide adequate glycemic outcomes in 23% and 25–28% of participants with GDM, respectively (76,77).

Sulfonylureas

Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels (76,77). In meta-analyses and systematic reviews, glyburide was associated with a higher rate of neonatal hypoglycemia, macrosomia, and increased neonatal abdominal circumference than insulin or metformin (78,79).

Glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (80). Long-term safety data for offspring exposed to glyburide are not available (80).

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews and RCTs (78,81–83). However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (84,85). In the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study's analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin for the treatment of GDM in the Auckland cohort were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin (86). This difference was not found in the Adelaide cohort. In one RCT of metformin use in pregnancy for polycystic ovary syndrome, follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin (87). A follow-up study at 5–10 years showed that the offspring had higher BMI, weight-to-height ratios, waist circumferences, and a borderline increase in fat mass (88,89). A meta-analysis demonstrated that metformin exposure resulted in smaller neonates with an acceleration of postnatal growth, resulting in higher BMI in childhood (88). Follow-up of offspring from the Metformin in Women with Type 2 Diabetes in Pregnancy (MiTy Kids) trial showed no differences in anthropometrics of children at 24 months (90).

Randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in individuals with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (91), and there is no evidence-based need to continue metformin in these individuals (92–94).

There are some people with GDM requiring medical therapy who may not be able to use insulin safely or effectively during pregnancy due to cost, language barriers, comprehension, or cultural influences. Oral agents may be an alternative for these individuals after discussing the known risks and the need for more long-term safety data in offspring. However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in pregnant people with hypertension or preeclampsia or those at risk for intrauterine growth restriction (90,95,96).

Insulin

Insulin use should follow the guidelines below. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies, and neither has been shown to be superior to the other during pregnancy (97).

MANAGEMENT OF PREEXISTING TYPE 1 DIABETES AND TYPE 2 DIABETES IN PREGNANCY

Recommendations

15.18 Insulin should be used to manage type 1 diabetes in pregnancy. **A** Insulin is the preferred agent for the management of type 2 diabetes in pregnancy. **B**

15.19 Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes. **C**

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent blood glucose monitoring. Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including a maternal-fetal medicine specialist, endocrinologist or other health care professional experienced in managing pregnancy and preexisting diabetes, RDN, diabetes care and education specialist, and social worker, as needed) is recommended if this resource is available. When a single specialized center is not available, providing a interprofessional team approach through interprofessional team members at different centers may still be beneficial.

None of the currently available human insulin preparations have been demonstrated to cross the placenta (93–98). Insulins studied in RCTs are preferred (97,99–103) over those studied in cohort studies (104), which are preferred over those studied in case reports only.

While many health care professionals prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections (105,106). None of the current automated insulin delivery (AID) systems approved by the U.S. Food and Drug Administration (FDA) have algorithms set to achieve pregnancy goals. It may be appropriate to continue or initiate AID therapy in carefully selected pregnant individuals with type 1 diabetes in the setting of using assistive techniques with expert guidance (107). Assessments of potential candidates for AID wear in pregnancy should include relevant parameters such as glycemic levels, presence or absence of severe hypoglycemic or hyperglycemic events, ability or comfort in engaging with diabetes technology, psychosocial determinants, cost, individual preference, and other factors as relevant. In addition, individuals who use AID systems that do not have pregnancy-specific glucose targets often benefit from assistive techniques for pump management as determined by expert guidance from an experienced interprofessional team (107). Partial closed-loop therapy, such as predictive low-glucose suspend (PLGS) technology, has been shown in nonpregnant people to be better than sensor-augmented insulin pumps (SAP) for reducing low glucose values (108). It may be suited for pregnancy because the predictive low-glucose threshold for suspending insulin is in the range of premeal and overnight glucose value targets in pregnancy and may allow for more aggressive prandial dosing. See SENSOR-AUGMENTED PUMPS and AUTOMATED INSULIN DELIVERY SYSTEMS in Section 7, "Diabetes Technology," for more information on these systems.

Type 1 Diabetes

Pregnant individuals with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all pregnant people, have altered counter-regulatory response in pregnancy that may decrease hypoglycemia awareness. Education for people with diabetes and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help prevent and manage hypoglycemia risk. Insulin resistance drops rapidly with the delivery of the placenta.

Pregnancy is a ketogenic state, and people with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis (DKA) at lower blood glucose levels than in the nonpregnant state. Pregnant people with type 1 diabetes should be advised to obtain ketone test strips and receive education on DKA prevention and detection. DKA carries a high risk of stillbirth. Those in DKA who are unable to eat often require 10% dextrose with an insulin drip to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester in order to resolve their ketosis.

Retinopathy is a special concern in pregnancy. The necessary rapid implementation of euglycemia in the setting of retinopathy is associated with worsening of retinopathy (109). Meta-analyses have also demonstrated a high risk of new-onset retinopathy and progression of existing retinopathy in pregnant individuals with type 1 or type 2 diabetes (110,111).

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for people with overweight is 15–25 lb (6.8–11.3 kg) and for those with obesity is 10–20 lb (4.5–9.1 kg) (67). There are no adequate data on optimal weight gain versus weight maintenance in pregnant people with BMI >35 kg/m^2; however, losing weight is not recommended because of the increased risk of small-for-gestational age infants (21).

Optimal glycemic goals are often easier to achieve during pregnancy with type 2 diabetes than with type 1 diabetes but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. Insulin is the preferred treatment for type 2 diabetes in pregnancy. An RCT of metformin added to insulin for the treatment of type 2 diabetes found less maternal weight gain and fewer cesarean births. There were fewer macrosomic neonates, but there was a doubling of small-for-gestational-age neonates (112). As in type 1 diabetes, insulin requirements drop dramatically after delivery.

The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes compared with type 1 diabetes, even if diabetes is better managed and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in those with type 2 diabetes, compared with the first trimester in those with type 1 diabetes (113,114).

PREECLAMPSIA AND ASPIRIN

Recommendation

15.20 Pregnant individuals with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia. **E** A dosage of 162 mg/day may be acceptable; **E** currently, in the U.S., low-dose aspirin is available in 81-mg tablets.

Diabetes in pregnancy is associated with an increased risk of preeclampsia (115). The U.S. Preventive Services Task Force recommends using low-dose aspirin (81 mg/day) as a preventive medication at 12 weeks of gestation in individuals at high risk for preeclampsia, such as those with type 1 or type 2 diabetes (116). However, a meta-analysis and an additional trial demonstrate that low-dose aspirin $<$100 mg is not effective in reducing preeclampsia. Low-dose aspirin $>$100 mg is required (117–119). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (120). There are insufficient data about whether the use of aspirin specifically in pregnant people with preexisting diabetes ultimately reduces the incidence of preeclampsia (121,122), although a meta-analysis showed that preeclampsia reductions occurred with aspirin administration in high-risk groups overall (115). Individuals with GDM may be candidates for aspirin therapy for preeclampsia prevention if they have a single high risk factor, such as chronic hypertension or an autoimmune disease, or multiple moderate risk factors, such as being nulliparous, having obesity, being age $\geq$35 years, or other factors per the U.S. Preventive Services Task Force (116). More studies are needed to assess the long-term effects of prenatal aspirin exposure on offspring (121).

PREGNANCY AND DRUG CONSIDERATIONS

Recommendations

15.21 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational-age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be deintensified for blood pressure $<$90/60 mmHg. **E** A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

15.22 Potentially harmful medications in pregnancy (i.e., ACE inhibitors, angiotensin receptor blockers, statins) should be stopped prior to conception and avoided in sexually active individuals of childbearing potential who are not using reliable contraception. **B**

In normal pregnancy, blood pressure is lower than in the nonpregnant state. The Chronic Hypertension and Pregnancy (CHAP) Trial Consortium's RCT on treatment for mild chronic hypertension during pregnancy demonstrated that a blood pressure of 140/90 mmHg, as the threshold for initiation or titration of treatment, reduces the incidence of adverse pregnancy outcomes without compromising fetal growth (123). The CHAP Consortium's study mitigates concerns about small-for-gestational-age birth weight. Attained mean ± SD blood pressure measurements in the treated versus untreated groups were systolic 129.5 ± 10.0 vs. 132.6 ± 10.1 mmHg (between-group difference $-$3.11 [95% CI $-$3.95 to 2.28]) and diastolic 79.1 ± 7.4 vs. 81.5 ± 8.0 mmHg ($-$2.33 [95% CI $-$2.97 to 0.04]) (123). Individuals with diabetes had an even better composite outcome score than those without diabetes (123).

As a result of the CHAP study, ACOG issued a Practice Advisory recommending a blood pressure of 140/90 mmHg as the threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy (124) rather than their previously recommended threshold of 160/110 mmHg (125).

The CHAP study provides additional guidance for the management of hypertension in pregnancy. Data from the previously published Control of Hypertension in Pregnancy Study (CHIPS) supports a target blood pressure goal of 110–135/85 mmHg to reduce the risk of uncontrolled maternal hypertension and minimize impaired fetal growth (125–127). The 2015 study (126) excluded pregnancies complicated by preexisting diabetes, and only 6% of participants had GDM at enrollment. There was no difference in pregnancy loss, neonatal care, or other neonatal outcomes between the groups with tighter versus less tight control of hypertension (126).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, pulmonary hypoplasia, and intrauterine growth restriction (23).

A large study found that after adjusting for confounders, first trimester ACE inhibitor exposure does not appear to be associated with congenital malformations (128). However, ACE inhibitors and angiotensin receptor blockers should be stopped as soon as possible in the first trimester to avoid second and third trimester fetopathy (128). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine, labetalol, diltiazem, clonidine, and prazosin. Atenolol is not recommended, but other β-blockers may be used, if necessary. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (129). On the basis of available evidence, statins should also be avoided in pregnancy (130).

See pregnancy and antihypertensive medications in Section 10, "Cardiovascular Disease and Risk Management," for more information on managing blood pressure in pregnancy.

POSTPARTUM CARE

Recommendations

15.23 Insulin resistance decreases dramatically immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the prepregnancy requirements for the initial few days postpartum. **C**

15.24 A contraceptive plan should be discussed and implemented with all people with diabetes of childbearing potential. **A**

15.25 Screen individuals with a recent history of GDM at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

15.26 Individuals with overweight/obesity and a history of GDM found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

15.27 Breastfeeding efforts are recommended for all individuals with diabetes. **A** Breastfeeding is recommended for individuals with a history of GDM for multiple benefits, **A** including a reduced risk for type 2 diabetes later in life. **B**

15.28 Individuals with a history of GDM should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years. **B**

15.29 Individuals with a history of GDM should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. **E**

15.30 Postpartum care should include psychosocial assessment and support for self-care. **E**

Gestational Diabetes Mellitus Postpartum Care

Because GDM often represents previously undiagnosed prediabetes, type 2 diabetes, maturity-onset diabetes of the young, or even developing type 1 diabetes, individuals with GDM should be tested for persistent diabetes or prediabetes at 4–12 weeks postpartum with a fasting 75-g OGTT using nonpregnancy criteria as outlined in Section 2, “Diagnosis and Classification of Diabetes,” specifically **Tables 2.1 and 2.2**. The OGTT is recommended over A1C at 4–12 weeks postpartum because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy, by blood loss at delivery, or by the preceding 3-month glucose profile. The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. In the absence of unequivocal hyperglycemia, a positive screen for diabetes requires two abnormal values. If both the fasting plasma glucose ($\geq$126 mg/dL [$\geq$7.0 mmol/L]) and 2-h plasma glucose ($\geq$200 mg/dL [$\geq$11.1 mmol/L]) are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets diabetes criteria, the test should be repeated to confirm that the abnormality persists. OGTT testing immediately postpartum, while still hospitalized, has demonstrated improved engagement in testing but also variably reduced sensitivity to the diagnosis of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes (131,132).

Individuals with a history of GDM should have ongoing screening for prediabetes or type 2 diabetes every 1–3 years, even if the results of the initial 4–12 week postpartum 75-g OGTT are normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 75-g OGTT using thresholds for nonpregnant individuals).

Individuals with a history of GDM have an increased lifetime maternal risk for diabetes estimated at 50–60% (133,134), and those with GDM have a 10-fold increased risk of developing type 2 diabetes compared with those without GDM (133). Absolute risk of developing type 2 diabetes after GDM increases linearly through a person’s lifetime, being approximately 20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years (134). In the prospective Nurses’ Health Study II (NHS II), subsequent diabetes risk after a history of GDM was significantly lower in those who followed healthy eating patterns (135). Adjusting for BMI attenuated this association moderately, but not completely. Interpregnancy weight gain is associated with increased risk of adverse pregnancy outcomes (136) and higher risk of GDM, while in people with BMI $>$25 kg/m^2, weight loss is associated with lower risk of developing GDM in the subsequent pregnancy (137). Development of type 2 diabetes is 18% higher per unit of BMI increase from prepregnancy BMI at follow-up, highlighting the importance of effective weight management after GDM (138). In addition, postdelivery lifestyle interventions are effective in reducing risk of type 2 diabetes (139).

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in individuals with prediabetes and a history of GDM. Only five to six individuals with prediabetes and a history of GDM need to be treated with either intervention to prevent one case of diabetes over 3 years (140). In these individuals, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (141). If the pregnancy has motivated the adoption of healthy nutrition, building on these gains to support weight loss is recommended in the postpartum period. (See Section 3, “Prevention or Delay of Diabetes and Associated Comorbidities.”)

Individuals with prediabetes or a history of GDM will need preconception evaluation for as long as they have childbearing potential.

Preexisting Type 1 and Type 2 Diabetes Postpartum Care

Insulin sensitivity increases dramatically with the delivery of the placenta. In one study, insulin requirements in the immediate postpartum period are roughly 34% lower than prepregnancy insulin requirements (142). Insulin sensitivity then returns to prepregnancy levels over the following 1–2 weeks. For individuals taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules (143).

Lactation

Considering the immediate nutritional and immunological benefits of breastfeeding for the baby, all mothers, including those with diabetes, should be supported in attempts to breastfeed. An analysis of 28 systematic reviews and meta-analyses of associations between breastfeeding and outcomes in children found that breastfeeding was associated with numerous health benefits for children such as reduced infant mortality due to infectious diseases at $<$6 months of age (odds ratio [OR] 0.22–0.59 across studies), reduced respiratory infections in children aged $<$2 years, and reduced asthma or wheezing in children aged 5–18 years (OR 0.91, 0.85–0.98) (144). The same analysis found that breastfeeding was associated with improved maternal health outcomes including reduced risks of breast cancer (OR 0.81 [95% CI 0.77–0.86]), ovarian cancer (OR 0.70 [95% CI 0.64–0.75]), and type 2 diabetes (OR 0.68 [95% CI 0.57–0.82]). Breastfeeding may also confer longer-term metabolic benefits to both mother (145) and offspring (146). Breastfeeding reduces the risk of developing type 2 diabetes in mothers with previous GDM (145). It may improve the metabolic risk factors of offspring, but more studies are needed (147). However, lactation can increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

Contraception

A major barrier to effective preconception care is the fact that the majority of pregnancies are unplanned. Planning pregnancy is critical in individuals with preexisting diabetes to achieve the optimal glycemic goals necessary to prevent congenital malformations and reduce the risk of other complications. Therefore, all individuals with diabetes of childbearing potential should have family planning options reviewed at regular intervals to make sure that effective contraception is implemented and maintained. This applies to individuals in the immediate postpartum period. Individuals with diabetes have the same contraception options and recommendations as those without diabetes. Long-acting, reversible contraception may be ideal for individuals with diabetes and childbearing potential. The risk of an unplanned pregnancy outweighs the risk of any currently available contraception option.

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16. Diabetes Care in the Hospital: *Standards of Care in Diabetes—2024*

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*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Among hospitalized individuals, hyperglycemia, hypoglycemia, and glucose variability are associated with adverse outcomes, including increased morbidity and mortality (1). Identification and careful management of people with diabetes and dysglycemia during hospitalization has direct and immediate benefits. Diabetes management in the inpatient setting is facilitated by identification and treatment of hyperglycemia prior to elective procedures, a dedicated inpatient diabetes management service applying validated standards of care, and a proactive transition plan for outpatient diabetes care with timely prearranged follow-up appointments. These steps can improve outcomes, shorten hospital stays, and reduce the need for readmission and emergency department visits. For older hospitalized individuals or for people with diabetes in long-term care facilities, please see Section 13, "Older Adults."

HOSPITAL CARE DELIVERY STANDARDS

Recommendations

16.1 Perform an A1C test on all people with diabetes or hyperglycemia (random blood glucose $>$140 mg/dL [$>$7.8 mmol/L]) admitted to the hospital if no A1C test result is available from the prior 3 months. **B**

16.2 Institutions should implement protocols using validated written or computerized provider order entry sets for management of dysglycemia in the hospital (including emergency department, intensive care unit [ICU] and non-ICU wards, gynecology-obstetrics/delivery units, dialysis suites, and behavioral health units) that allow for a personalized approach, including glucose monitoring, insulin and/or noninsulin therapy, hypoglycemia management, diabetes self-management education, nutrition recommendations, and transitions of care. **B**

Considerations on Admission

High-quality hospital care for diabetes requires standards for care delivery, which are best implemented using structured order sets and quality improvement strategies for

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**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

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process improvement. Unfortunately, "best practice" protocols, reviews, and guidelines are inconsistently implemented within hospitals (2). To correct this, medical centers striving for optimal inpatient diabetes treatment should establish protocols and structured order sets, which include computerized provider order entry (CPOE). Institutions are encouraged to perform audits regularly to monitor proper use and institute educational/training programs to keep staff up to date.

Initial evaluation should state the type of diabetes (i.e., type 1, type 2, gestational, pancreatogenic, drug related, or nutrition related) when it is known. Because inpatient treatment and discharge planning are more effective when preadmission glycemia is considered, A1C should be measured for all people with diabetes or dysglycemia admitted to the hospital if no A1C test result is available from the previous 3 months (3–6). In addition, diabetes self-management knowledge and behaviors should be assessed on admission, and diabetes self-management education provided (if available), especially if a new treatment plan is being considered. Diabetes self-management education should include knowledge and survival skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia (7). Evidence supports preadmission treatment of hyperglycemia in people scheduled for elective surgery as an effective means of reducing adverse outcomes (8–11).

The National Academy of Medicine recommends CPOE to prevent medication-related errors and to increase medication administration efficiency (12). Systematic reviews of randomized controlled trials using computerized advice to improve glycemic outcomes in the hospital found significant improvement in the percentage of time individuals spent in the glycemic goal range, lower mean blood glucose levels, and no increase in hypoglycemia (13). Where feasible, there should be structured order sets that provide computerized guidance for glycemic management. Insulin dosing algorithms using machine learning and data in the electronic health record (EHR) currently in development show promise for predicting insulin requirements during hospitalization (14).

Diabetes Care Specialists in the Hospital

Recommendation

16.3 When caring for hospitalized people with diabetes (with an existing or new diagnosis) or stress hyperglycemia, consult with a specialized diabetes or glucose management team when accessible. **B**

Care provided by appropriately trained specialists or specialty teams may reduce the length of stay and improve glycemic and other clinical outcomes (15,16). In addition, the increased risk of 30-day readmission following hospitalization that has been attributed to diabetes can be reduced, and costs saved, when inpatient care is provided by a specialized diabetes management team (15,17,18). In a cross-sectional study comparing usual care to specialists reviewing diabetes cases and making recommendations virtually through the EHR, rates of both hyperglycemia and hypoglycemia were reduced by 30–40% (19). Providing inpatient diabetes self-management education and developing a diabetes discharge plan that includes continued access to diabetes medications and supplies and ongoing education and support are key strategies to improve outcomes (20,21). Details of diabetes care team composition and other resources are available from the Joint Commission accreditation program for the hospital care of diabetes, from the Society of Hospital Medicine workbook, and from the Joint British Diabetes Societies (JBDS) for Inpatient Care Group (22–24).

GLYCEMIC GOALS IN HOSPITALIZED ADULTS

Recommendations

16.4 Insulin **A** and/or other therapies **B** should be initiated or intensified for treatment of persistent hyperglycemia starting at a threshold of ≥180 mg/dL (≥10.0 mmol/L) (confirmed on two occasions within 24 h) for noncritically ill (non-ICU) individuals. **A**

16.5a Once therapy is initiated, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill (ICU) individuals with hyperglycemia. **A**

16.5b More stringent glycemic goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected critically ill individuals and are acceptable if they can be achieved without significant hypoglycemia. **B**

Standard Definitions of Glucose Abnormalities

Hyperglycemia in hospitalized individuals is defined as blood glucose levels >140 mg/dL (>7.8 mmol/L) (2). An admission A1C value ≥6.5% (≥48 mmol/mol) suggests that the onset of diabetes preceded hospitalization (see Section 2, "Diagnosis and Classification of Diabetes"). Level 1 hypoglycemia is defined as a glucose concentration of 54–69 mg/dL (3.0–3.8 mmol/L). Level 2 hypoglycemia is defined as a glucose concentration <54 mg/dL (<3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms. Level 3 hypoglycemia is defined as a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery (**Table 6.4**) (25,26). Levels 2 and 3 require immediate intervention and correction of low blood glucose. Prompt treatment of level 1 hypoglycemia is recommended as an effort to prevent progression to more significant level 2 and level 3 hypoglycemia.

Glycemic Goals

In a landmark clinical trial conducted in a surgical intensive care unit (ICU), Van den Berghe et al. (27) demonstrated that an intensive intravenous insulin protocol with a glycemic goal of 80–110 mg/dL (4.4–6.1 mmol/L) reduced mortality by 40% compared with a standard approach of a glycemic goal of 180–215 mg/dL (10–12 mmol/L) in critically ill hospitalized individuals with recent surgery. This study provided evidence that active treatment to lower blood glucose in hospitalized individuals could have immediate benefits. However, a large, multicenter follow-up study in critically ill hospitalized individuals, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (28), led to a reconsideration of the optimal glucose lowering goal in critical illness. In this trial, critically ill individuals randomized to intensive glycemic management (80–110 mg/dL [4.4–6.1 mmol/L]) derived no significant treatment advantage compared with a group with more moderate glycemic goals (140–180 mg/dL [7.8–10.0 mmol/L]) and had slightly but significantly higher mortality (27.5% vs. 25%). The intensively treated group had 10- to 15-fold greater rates of hypoglycemia, which may have contributed to the adverse outcomes noted. The findings from the NICE-SUGAR trial, supported by several meta-analyses and a randomized controlled trial, showed higher rates of hypoglycemia and an increase in mortality with more aggressive glycemic management goals compared with moderate glycemic goals (29–31). Based on these results, insulin and/or other therapies should be initiated for the treatment of persistent hyperglycemia ≥180 mg/dL (≥10.0 mmol/L). Once therapy is initiated, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill individuals with hyperglycemia. Although not as well supported by data from randomized controlled trials, these recommendations have been extended to hospitalized individuals without critical illness. More stringent glycemic goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected individuals (e.g., critically ill individuals undergoing surgery) if it can be achieved without significant hypoglycemia (32,33).

For inpatient management of hyperglycemia in noncritical care settings, a glycemic goal of 100–180 mg/dL (5.6–10.0 mmol/L) is recommended, whether it is new hyperglycemia (e.g., newly diagnosed diabetes or stress hyperglycemia) or hyperglycemia related to diabetes prior to admission (2). It has been found that fasting glucose levels <100 mg/dL (<5.6 mmol/L) are predictors of hypoglycemia within the next 24 h (34). Glycemic levels up to 250 mg/dL (13.9 mmol/L) may be acceptable in selected populations (terminally ill individuals with short life expectancy, advanced kidney failure [and/or on dialysis], high risk for hypoglycemia, and/or labile glycemic excursions). In these individuals, less aggressive treatment goals that would help avoid symptomatic hypoglycemia and/or hyperglycemia are often appropriate. Clinical judgment combined with ongoing assessment of clinical status, including changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), may be incorporated into the day-to-day decisions regarding treatment dosing.

GLUCOSE MONITORING

In hospitalized individuals with diabetes who are eating, point-of-care (POC) blood glucose monitoring should be performed before meals; in those not eating, glucose monitoring is advised every 4–6 h (26). More frequent POC blood glucose monitoring ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin therapy.

Hospital blood glucose monitoring should be performed with U.S. Food and Drug Administration (FDA)–approved POC hospital-calibrated glucose monitoring systems (35). POC blood glucose meters are not as accurate or as precise as laboratory glucose analyzers, and capillary blood glucose readings are subject to artifacts due to perfusion, edema, anemia/erythrocytosis, and several medications commonly used in the hospital (35) (**Table 7.1**). The FDA has established standards for capillary (finger-stick) POC glucose monitoring in the hospital (35). The balance between analytic requirements (e.g., accuracy, precision, and interference) and clinical requirements (e.g., rapidity, simplicity, and POC) has not been uniformly resolved (35–38), and most hospitals have arrived at their own policies to balance these parameters. It is critically important that devices selected for in-hospital use, and the workflow through which they are applied, undergo careful analysis of performance and reliability and ongoing quality assessments (38). Recent studies indicate that POC measures provide adequate information for usual practice, with only rare instances where care has been compromised (36,37). Best practice dictates that any glucose result that does not correlate with the individual's clinical status should be confirmed by measuring a sample in the clinical laboratory, particularly for asymptomatic hypoglycemic events.

Continuous Glucose Monitoring

Recommendations

16.6 In people with diabetes using a personal continuous glucose monitoring (CGM) device, the use of CGM should be continued during hospitalization if clinically appropriate, with confirmatory point-of-care (POC) glucose measurements for insulin dosing decisions and hypoglycemia assessment, if resources and training are available, and according to an institutional protocol. **B**

16.7 For people with diabetes using an automated insulin delivery (AID) system along with CGM, the use of AID and CGM should be continued during hospitalization if clinically appropriate, with confirmatory POC blood glucose measurements for insulin dosing decisions and hypoglycemia assessment, if resources and training are available, and according to an institutional protocol. **C**

Several studies have demonstrated that inpatient use of continuous glucose monitoring (CGM) has advantages over POC glucose monitoring in detecting hypoglycemia, particularly nocturnal, prolonged and/or asymptomatic hypoglycemia (39–41), and in reducing recurrent hypoglycemia (42,43). However, at this time, initiating use of a new CGM device has not been approved by the FDA. During the coronavirus disease 2019 (COVID-19) pandemic, many institutions used CGM in ICU and non-ICU settings, with the aim of minimizing exposure time and saving personal protective equipment, under an FDA policy of enforcement discretion (44,45). Data on the safety and efficacy of real-time CGM use in the hospital, particularly with implementation of remote monitoring (e.g., a glucose telemetry system), is growing (42,43,45–50).

Continuation of personal CGM device use, particularly for people with type 1 or type 2 diabetes treated with intensive therapy at increased risk for hypoglycemia during hospitalization, is recommended. Confirmatory POC capillary glucose testing, using hospital-calibrated glucose meters, is recommended for insulin dosing and hypoglycemia assessment (e.g., hybrid testing protocols) (51). People with diabetes should be counseled about meaningful use of trend arrows and alarms and about notifying nursing staff for confirmation of these events with POC capillary glucose testing. Similarly, continuation of AID systems should be supported during hospitalization, when clinically appropriate, and with proper staff training and supervision (41,45). Observational studies have demonstrated improvements in patient satisfaction and improved detection of glycemic excursions (40,47). If the reason for admission is suspected to be related to device malfunction or lack of adequate education/training or use, consultation with the endocrinology/

diabetes care team or diabetes care and education specialists, if available, is recommended. Hospitals are encouraged to develop institutional policies and have trained personnel with knowledge of diabetes technology. Recent review articles provide details on accuracy, interferences, precautions, and contraindications of diabetes technology devices in the hospital setting (50,51).

For more information on CGM, see Section 7, "Diabetes Technology."

GLUCOSE-LOWERING TREATMENT IN HOSPITALIZED PATIENTS

An individualized approach for glycemic management is encouraged throughout the hospital stay and should take into consideration several predictive factors for achieving glycemic goals, such as prior home use and dose of insulin or noninsulin therapy, expected level of insulin resistance, prior A1C, current glucose levels, oral intake, and duration of diabetes.

Insulin Therapy

Recommendations

16.8 Basal insulin or a basal plus bolus correction insulin plan is the preferred treatment for noncritically ill hospitalized individuals with poor oral intake or those who are taking nothing by mouth. **A**

16.9 An insulin plan with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized individuals with adequate nutritional intake. **A**

16.10 Sole use of a correction or supplemental insulin without basal insulin (formerly referred to as a sliding scale) in the inpatient setting is discouraged. **A**

Critical Care Setting

Continuous intravenous insulin infusion is the most effective method for achieving specific glycemic goals and avoiding hypoglycemia in the critical care setting. Intravenous insulin infusions should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin infusion rate based on glycemic fluctuations and immediate past and current insulin infusion rates (52). For diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) management, continuous intravenous insulin infusion is given for correction of hyperglycemia, hyperketonemia, and acid-base disorder following a fixed-rate intravenous insulin infusion (53) or nurse-driven protocol with a variable rate based on glucose values (54). Individuals with mild and uncomplicated DKA can be managed with subcutaneous rapid-acting insulin doses given every 1–2 h (55).

Noncritical Care Setting

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized individuals. In certain circumstances, it may be appropriate to continue home oral glucose-lowering medications, such as dipeptidyl peptidase 4 inhibitors (DPP-4i) (52,56). If oral medications are held in the hospital but will be reinstated after discharge, there should be a protocol for guiding resumption of home medications 1–2 days prior to discharge. For people taking insulin, several reports indicate that inpatient use of insulin pens is safe and may improve nurse satisfaction when safety protocols, including nursing education, are in place to guarantee single-person use (57–61).

Outside of critical care units, scheduled subcutaneous insulin orders are recommended for the management of hyperglycemia in people with diabetes and hyperglycemia. Use of insulin analogs or human insulin results in similar glycemic outcomes in the hospital setting but may increase severe hypoglycemic events (62). The use of subcutaneous rapid- or short-acting insulin before meals, or every 4–6 h if no meals are given or if the individual is receiving continuous enteral/parenteral nutrition, is indicated to correct or prevent hyperglycemia. Basal insulin, or a basal plus bolus correction schedule, is the preferred treatment for noncritically ill hospitalized individuals with inadequate or restricted oral intake. An insulin schedule with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized people with diabetes with adequate nutritional intake.

A randomized controlled trial has shown that basal plus bolus treatment improved glycemic outcomes and reduced hospital complications compared with a correction or supplemental insulin without basal insulin (formerly known as sliding scale) for people with type 2 diabetes admitted for general surgery (63). Prolonged use of correction or supplemental insulin without basal insulin as the sole treatment of hyperglycemia is strongly discouraged in the inpatient setting, with the exception of people with type 2 diabetes in noncritical care with mild hyperglycemia (2,64,65).

A prospective randomized inpatient study of 70/30 intermediate-acting (NPH)/regular insulin mixture versus basal-bolus therapy showed comparable glycemic outcomes but significantly increased hypoglycemia in the group receiving insulin mixture (66). Therefore, insulin mixtures such as 75/25, 70/30, or 50/50 insulins are not routinely recommended for in-hospital use.

Data on the use of glargine U-300 and degludec U-100 or U-200 in the inpatient and perioperative settings are limited. A few studies have shown that they demonstrated similar efficacy and safety compared with glargine U-100 (67–69). At this time, there is no available evidence for weekly insulin use in hospital or surgical settings.

Type 1 Diabetes

For people with type 1 diabetes, dosing insulin based solely on premeal glucose levels does not account for basal insulin requirements or caloric intake, increasing the risk of both hypoglycemia and hyperglycemia. Typically, basal insulin dosing is based on body weight and expected sensitivity to insulin, with some evidence that people with renal insufficiency should be treated with lower insulin doses (70,71). An insulin schedule with basal and correction components is necessary for all hospitalized individuals with type 1 diabetes, even when taking nothing by mouth, with the addition of prandial insulin when eating. Policies and best practice alerts in the EHR should be put in place to ensure that basal insulin (given subcutaneously, via insulin pump or by insulin infusion) is not held for people with type 1 diabetes, especially during care transitions, and that ongoing prescriber and nursing education is provided (60).

Transitioning From Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is recommended, as it is associated with less morbidity and lower costs of care. Subcutaneous basal insulin should be given 2 h before intravenous infusion is discontinued, with the aim of minimizing rebound hyperglycemia (2,72,73).

Emerging data from several studies show that the administration of a low dose (0.15–0.3 units/kg) of basal insulin analog in addition to intravenous insulin infusion may reduce the duration of insulin infusion and length of hospital stay and prevent rebound hyperglycemia without increased risk of hypoglycemia (74–76).

For transitioning, the total daily dose of subcutaneous insulin can be calculated based on the insulin infusion rate during the prior 6–8 h when stable glycemic goals were achieved, based on prior home insulin dose, or following a weight-based approach (72,73). For people being transitioned to concentrated insulin (U-200, U-300, or U-500) in the inpatient setting, it is important to ensure correct dosing by using a separate pen or vial for each person and by meticulous pharmacy and nursing supervision of the dose administered (77,78).

Noninsulin Therapies

Recommendation

16.11 For people with type 2 diabetes hospitalized with heart failure, it is recommended that use of a sodium–glucose cotransporter 2 inhibitor be initiated or continued during hospitalization and upon discharge, if there are no contraindications and after recovery from the acute illness. **A**

The safety and efficacy of noninsulin glucose-lowering therapies in the hospital setting has expanded recently (79–83). A randomized trial and an observational study have demonstrated the safety and efficacy of DPP-4i in specific groups of hospitalized people with diabetes (84,85). The use of DPP-4i with or without basal insulin may be a safer and simpler plan for people with mild to moderate hyperglycemia on admission (e.g., admission glucose <180–200 mg/dL), with reduced risk of hypoglycemia (79,85,86). Of note, the FDA states that health care professionals should consider discontinuing saxagliptin and alogliptin in people who develop heart failure (87). Data on the inpatient use of glucagon-like peptide 1 (GLP-1) receptor agonists are still mostly limited to research studies and select populations that are medically stable (83).

For people with type 2 diabetes hospitalized with heart failure, it is recommended that use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor be initiated or continued during hospitalization and upon discharge, if there are no contraindications and after recovery from the acute illness (88,89). SGLT2 inhibitors should be avoided in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures (90–93). Proactive adjustment of diuretic dosing is recommended during hospitalization and/or discharge, especially in collaboration with a cardiology/heart failure consult team (90–93). The FDA has warned that SGLT2 inhibitors should be stopped 3 days before scheduled surgeries (4 days in the case of ertugliflozin) (94).

HYPOGLYCEMIA

Recommendations

16.12 A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system. A plan for preventing and treating hypoglycemia should be established for each individual. Episodes of hypoglycemia in the hospital should be documented in the electronic health record and tracked for quality assessment and quality improvement. **E**

16.13 Treatment plans should be reviewed and changed as necessary to prevent hypoglycemia and recurrent hypoglycemia when a blood glucose value of <70 mg/dL (<3.9 mmol/L) is documented. **C**

People with or without diabetes may experience hypoglycemia in the hospital setting. While hypoglycemia is associated with increased mortality (95,96), in many cases, it is a marker of an underlying disease rather than the cause of fatality. However, hypoglycemia is a severe consequence of dysregulated metabolism and/or diabetes treatment, and it is imperative that it be minimized during hospitalization. Many episodes of inpatient hypoglycemia are preventable. A hypoglycemia prevention and management protocol should be adopted and implemented by each hospital or hospital system. A standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol should be in place to immediately address blood glucose levels <70 mg/dL (<3.9 mmol/L) (97,98). In addition, individualized plans for preventing and treating hypoglycemia for each individual should also be developed. An American Diabetes Association consensus statement recommends that an individual's treatment plan be reviewed any time a blood glucose value of <70 mg/dL (<3.9 mmol/L) occurs, as this level often predicts subsequent level 3 hypoglycemia (99). Episodes of hypoglycemia in the hospital should be documented in the EHR and tracked (1). A key strategy is embedding hypoglycemia treatment into all insulin and insulin infusion orders.

Inpatient Hypoglycemia: Risk Factors, Treatment, and Prevention

Insulin is one of the most common medications causing adverse events in hospitalized individuals. Errors in insulin dosing, missed doses, and/or administration errors including incorrect insulin type and incorrect timing of dose occur relatively frequently (100–102) and include prescriber (ordering), pharmacy (dispensing), and nursing (administration) errors. Common preventable sources of iatrogenic hypoglycemia are improper prescribing of other glucose-lowering medications and inappropriate management and follow-up of the first episode of hypoglycemia (103). Kidney failure is an important risk factor for hypoglycemia in the hospital (104), possibly as a result of decreased insulin clearance. Studies of "bundled" preventive therapies, including proactive surveillance of glycemic outliers and an interdisciplinary data-driven approach to glycemic management, showed that hypoglycemic episodes in the hospital could be reduced or prevented. Compared with baseline, studies found that hypoglycemic events decreased by 56–80% (98,105,106). The Joint Commission, a global quality improvement and patient safety in health care organization, recommends that all hypoglycemic episodes be evaluated for a root cause and the episodes be aggregated and reviewed to address systemic issues (23).

In addition to errors with insulin treatment, iatrogenic hypoglycemia may be induced by a sudden reduction of corticosteroid dose, reduced oral intake, emesis, inappropriate timing of short- or rapid-acting insulin doses in relation to meals, reduced infusion rate of intravenous dextrose, unexpected interruption of enteral or parenteral feedings, delayed or missed blood glucose checks, and altered ability of the individual to report symptoms (107).

Recent inpatient studies show promise for CGM as an early warning system to alert of impending hypoglycemia, offering an opportunity to mitigate it before it happens (46–49). The use of personal CGM and AID devices, such as insulin pumps that can automatically deliver correction doses and change basal delivery rates in real time, should be supported for ongoing use during hospitalization for individuals who are capable of using their devices safely and independently when proper oversight supervision is available. Hospitals should be encouraged to develop policies and protocols to support inpatient use of individual- and hospital-owned diabetes technology and have expert staff available for safe implementation and evaluation of continued use during the hospital stay (51). Hospital information technology teams are beginning to integrate CGM data into the EHR. The ability to download and interpret diabetes device data during hospitalization can inform insulin dosing during hospitalization and care transitions (41).

For more information on CGM, see Section 7, "Diabetes Technology."

Predictors of Hypoglycemia

In people with diabetes, it is well established that an episode of severe hypoglycemia increases the risk for a subsequent event, partly because of impaired counterregulation (108,109). In a study of hospitalized individuals, 84% of people who had an episode of severe hypoglycemia (defined as <40 mg/dL [<2.2 mmol/L]) had a preceding episode of hypoglycemia (<70 mg/dL [<3.9 mmol/L]) during the same admission (110). In another study of hypoglycemic episodes (defined as <50 mg/dL [<2.8 mmol/L]), 78% of individuals were taking basal insulin, with the incidence of hypoglycemia peaking between midnight and 6:00 A.M. Despite recognition of hypoglycemia, 75% of individuals did not have their dose of basal insulin changed before the next basal insulin administration (111).

Recently, several groups have developed algorithms to predict episodes of hypoglycemia in the inpatient setting (112,113). Models such as these are potentially important and, once validated for general use, could provide a valuable tool to reduce rates of hypoglycemia in the hospital. In one retrospective cohort study, a fasting blood glucose of <100 mg/dL was shown to be a predictor of next-day hypoglycemia (34).

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy in the hospital are to provide adequate calories to meet metabolic demands, optimize glycemic outcomes, address personal food preferences, and facilitate the creation of a discharge plan. The American Diabetes Association does not endorse any single meal plan or specified percentages of macronutrients. Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use. Controlled carbohydrate meal plans, where the amount of carbohydrate on each meal tray is calculated, are preferred by many hospitals, as they facilitate matching the prandial insulin dose to the amount of carbohydrate given (114). Orders should also indicate that the meal delivery and nutritional insulin coverage should be coordinated, as their variability often creates the possibility of hyperglycemic and hypoglycemic events (20). Some hospitals offer "meals on demand," where individuals may order meals from the menu at any time during the day. This option improves patient satisfaction but complicates insulin–meal coordination and can lead to insulin stacking if meals are too close together. Finally, if the hospital food service supports carbohydrate counting, this option should be made available to people with diabetes counting carbohydrates at home and people wearing insulin pumps (115,116).

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for specific individuals who wish to continue to perform self-care while acutely ill (117–119). Candidates include children with parental supervision, adolescents, and adults who successfully perform diabetes self-management at home and whose cognitive and physical skills needed to successfully self-administer insulin and perform glucose monitoring are not compromised (7,41). In addition, they should have adequate oral intake, be proficient in carbohydrate estimation, take multiple daily insulin injections or wear insulin pumps, have stable insulin requirements, and understand sick-day management. If self-management is supported, a policy should include a requirement that people with diabetes and the care team agree that self-management is appropriate on a daily basis during hospitalization. Hospital personal medication policies may include guidance for people with diabetes who wish to take their own or hospital-dispensed insulin and noninsulin injectable medications during their hospital stay. A hospital policy for personal medication may consider a pharmacy exception on a case-by-case basis along with the care team. Pharmacy must verify any home medication and require a prescriber order for the individual to self-administer home or hospital-dispensed medication under the supervision of the registered nurse. If an insulin pump or CGM device is worn, hospital policy and procedures delineating guidelines for wearing an insulin pump and/or CGM device should be developed according to consensus guidelines, including the changing of insulin infusion sites and CGM glucose sensors (41,120,121). As outlined in Recommendations 7.33 and 7.34, people with diabetes wearing diabetes devices should be supported to continue them in an inpatient setting if they are assessed and deemed competent to perform self-care and proper supervision is available.

STANDARDS FOR SPECIAL SITUATIONS

Enteral/Parenteral Feedings

For individuals receiving enteral or parenteral feedings who require insulin, the insulin orders should include coverage of basal, prandial, and correctional needs (115,122,123). It is essential that people with type 1 diabetes continue to receive basal insulin even if feedings are discontinued.

Most adults receiving basal insulin should continue with their basal dose, while the insulin dose for the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g of carbohydrate in the enteral and parenteral formulas. Commercially available cans of enteral nutrition contain variable amounts of carbohydrates and may be infused at different rates.

All of this must be considered when calculating insulin doses to cover the nutritional component of enteral nutrition (116). Giving NPH insulin two or three times daily (every 8 or 12 h) to cover individual requirements is a reasonable option. Adjustments in insulin doses should be made frequently. Correctional insulin should also be administered subcutaneously every 6 h with regular human insulin. If enteral nutrition is interrupted, a dextrose infusion should be started immediately to prevent hypoglycemia and to allow time to determine more appropriate insulin doses.

For adults receiving enteral bolus feedings, approximately 1 unit of regular human insulin or rapid-acting insulin per every 10–15 g of carbohydrate should be given subcutaneously before each feeding. To mitigate any hyperglycemia, correctional insulin should be added as needed before each feeding.

In individuals receiving nocturnal tube feeding, NPH insulin administered along with the initiation of the feeding is a reasonable approach to cover this nutritional load.

For individuals receiving continuous peripheral or central parenteral nutrition, human regular insulin may be added to the solution, particularly if >20 units of correctional insulin have been required in the past 24 h. A starting dose of 1 unit of regular human insulin for every 10 g of dextrose has been recommended (105) and should be adjusted daily in the solution. Adding insulin to the parenteral nutrition bag is the safest way to prevent hypoglycemia if the parenteral nutrition is stopped or interrupted. Correctional insulin should be administered subcutaneously to address any hyperglycemia.

Because continuous enteral or parenteral nutrition results in a continuous postprandial state, efforts to bring blood glucose levels to below 140 mg/dL (7.8 mmol/L) substantially increase the risk of hypoglycemia in these individuals. For full enteral/parenteral feeding guidance, please refer to randomized controlled trials detailing this topic (122,124).

Glucocorticoid Therapy

The prevalence of consistent use of glucocorticoid therapy in hospitalized individuals can approach 10–15%, and these medications can induce hyperglycemia in 56–86% of these individuals with and without preexisting diabetes (125–127). If left untreated, this hyperglycemia increases mortality and morbidity risk, e.g., infections and cardiovascular events. Glucocorticoid type and duration of action must be considered in determining appropriate insulin treatments. Daily-ingested intermediate-acting glucocorticoids such as prednisone reach peak plasma levels in 4–6 h (128) but have pharmacologic actions that can last throughout the day. Individuals placed on morning steroid therapy have disproportionate hyperglycemia during the day but frequently reach blood glucose goals overnight regardless of treatment (125). In individuals on once- or twice-daily steroids, administering NPH insulin is a standard approach. NPH is usually administered in addition to daily basal-bolus insulin or in addition to oral glucose-lowering medications, depending on the type of diabetes and recent diabetes medication prior to starting steroids. Because NPH action peaks about 4–6 h after administration, it is recommended that it be administered concomitantly with intermediate-acting steroids (129). For long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use, long-acting basal insulin may be required to manage fasting blood glucose levels (53,130). For higher doses of glucocorticoids, increasing doses of prandial (if eating) and correction insulin, sometimes as much as 40–60% or more, are often needed in addition to basal insulin (131,132). A retrospective study found that increasing the ratio of insulin to steroids was positively associated with improved time in range (70–180 mg/dL); however, there was an increase in hypoglycemia (133). If insulin orders are initiated, daily adjustments based on levels of glycemia and anticipated changes in type, dosages, and duration of glucocorticoids, along with POC blood glucose monitoring, are critical to reducing hypoglycemia and hyperglycemia.

Perioperative Care

It is estimated that up to 20% of individuals undergoing general surgery have diabetes, and 23–60% have prediabetes or undiagnosed diabetes. Surgical stress and counterregulatory hormone release increase the risk of hyperglycemia as well as mortality, infection, and length of stay (134–136). There are little data available to guide care of people with diabetes through the perioperative period. To reduce surgical risk in people with diabetes, some institutions (135,137,138) have A1C cutoffs for elective surgeries, and some have developed optimization programs to lower A1C prior to surgery (134,135,137,138).

The following approach (134,135,137) may be considered:

1. A preoperative risk assessment should be performed for people with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
2. The A1C goal for elective surgeries should be <8% (<63.9 mmol/L) whenever possible.
3. The blood glucose goal in the perioperative period should be 100–180 mg/dL (5.6–10.0 mmol/L) (135) within 4 h of the surgery. CGM should not be used alone for glucose monitoring during surgery (138).
4. Metformin should be held on the day of surgery.
5. SGLT2 inhibitors should be discontinued 3–4 days before surgery.
6. Hold other oral glucose-lowering agents the morning of surgery or procedure and give one-half of NPH dose or 75–80% doses of long-acting analog insulin or adjust insulin pump basal rates based on the type of diabetes and clinical judgment.
7. Monitor blood glucose at least every 2–4 h while the individual takes nothing by mouth and dose with short- or rapid-acting insulin as needed.
8. There are little data on the safe use and/or influence of GLP-1 receptor agonists on glycemia and delayed gastric emptying in the perioperative period.
9. Stricter perioperative glycemic goals are not advised, as perioperative glycemic goals stricter than 80–180 mg/dL (4.4–10.0 mmol/L) may not improve outcomes and are associated with more hypoglycemia (137).
10. Compared with usual dosing, a reduction by 25% of basal insulin given the evening before surgery is more likely to achieve perioperative blood glucose goals with a lower risk for hypoglycemia (139).
11. In individuals undergoing noncardiac general surgery, basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with improved glycemic outcomes and lower rates of perioperative complications compared with the reactive, correction-only short- or rapid-acting insulin coverage alone with no basal insulin dosing (63,134,135).

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

There is considerable variability in the presentation of DKA and HHS, ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, and coma; therefore, individualization of treatment based on a careful clinical and laboratory assessment is needed (75,140–142).

Management goals include restoration of circulatory volume and tissue perfusion, resolution of ketoacidosis, and correction of electrolyte imbalance and acidosis. It is also essential to treat any correctable underlying cause of DKA, such as sepsis, myocardial infarction, or stroke. In critically ill and mentally obtunded individuals with DKA or HHS, continuous intravenous insulin is the standard of care. Successful transition from intravenous to subcutaneous insulin requires administration of basal insulin 2–4 h before the intravenous insulin is stopped to prevent recurrence of ketoacidosis and rebound hyperglycemia (72,73,140). Recent studies have reported that the administration of a low dose of basal insulin analog in addition to intravenous insulin infusion may prevent rebound hyperglycemia without increased risk of hypoglycemia (74–76,140). There is no significant difference in outcomes for intravenous human regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate DKA (143). Individuals with uncomplicated DKA may sometimes be treated with subcutaneous rapid-acting insulin analogs in the emergency department or step-down units (144). This approach may be safer and more cost-effective than treatment with intravenous insulin. If subcutaneous insulin administration is used, it is important to provide an adequate fluid replacement, frequent POC blood glucose monitoring, treatment of any concurrent infections, and appropriate follow-up to avoid recurrent DKA. Several studies have shown that the use of bicarbonate in people with DKA made no difference in the resolution of acidosis or time to discharge, and its use is generally not recommended (145). For further treatment information, refer to recent in-depth reviews (53, 107,146).

TRANSITION FROM THE HOSPITAL TO THE AMBULATORY SETTING

Recommendation

16.14 A structured discharge plan should be tailored to the individual with diabetes. **B**

A structured discharge plan tailored to the individual may reduce the length of hospital stay and readmission rates and increase satisfaction with the hospital experience (147). Multiple strategies are key, including diabetes self-management education prior to discharge, diabetes medication reconciliation with attention to access, and scheduled virtual and/or face-to-face follow-up visits after discharge. Discharge planning should begin at admission and be updated as individual needs change (148,149).

The transition from the acute care setting presents risks for all people with diabetes. Individuals may be discharged to varied settings, including home (with or without visiting nurse services), assisted living, rehabilitation, or skilled nursing facilities. For individuals discharged to home or assisted living, the optimal discharge plan will need to consider diabetes type and severity, effects of the illness on blood glucose levels, and the individual's circumstances, capabilities, and preferences (21,150,151). See Section 13, "Older Adults," for more information.

An outpatient follow-up visit with the primary care clinician, endocrinologist, or diabetes care and education specialist within 1 month of discharge is advised for all individuals experiencing hyperglycemia and/or hypoglycemia in the hospital. If glycemic medications are changed or glucose management is not optimal at discharge, an earlier appointment (in 1–2 weeks) is preferred, and frequent contact may be needed to avoid hyperglycemia and hypoglycemia. A discharge algorithm for glycemic medication adjustment, based on admission A1C, diabetes medications before admission, and insulin usage during hospitalization was found useful to guide treatment decisions and significantly improve A1C after discharge (4).

Clear communication with outpatient health care professionals directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the root cause of hyperglycemia (or the plan for determining the cause), related complications and comorbidities, and recommended treatments can assist outpatient health care professionals as they assume ongoing care.

The Agency for Healthcare Research and Quality recommends that, at a minimum, discharge plans include the following (152):

Medication Reconciliation

- Home and hospital medications must be cross-checked to ensure that no chronic medications are stopped and to ensure the safety of new and old prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the individual and care partners at or before discharge.

Structured Discharge Communication

- Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient health care professionals.
- Discharge summaries should be transmitted to the primary care clinician as soon as possible after discharge.
- Scheduling follow-up appointments prior to discharge with people with diabetes agreeing to the time and place increases the likelihood that they will attend.

It is recommended that the following areas of knowledge be reviewed and addressed before hospital discharge:

- Identification of the health care professionals who will provide diabetes care after discharge.
- Level of understanding related to the diabetes diagnosis, glucose monitoring, home glucose goals, and when to call a health care professional.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.
- Information on making healthy food choices at home and referral to an outpatient registered dietitian nutritionist or diabetes care and education specialist to guide individualization of the meal plan, if needed.
- When and how to take blood glucose-lowering medications, including insulin administration and noninsulin injectables.
- Sick-day management (21,151).
- Proper use and disposal of diabetes supplies, e.g., insulin pen, pen needles, syringes, and lancets.

People with diabetes must be provided with appropriate durable medical equipment, medications, supplies (e.g., blood glucose test strips or CGM sensors), prescriptions, and appropriate education at the time of discharge to avoid a potentially dangerous hiatus in care.

PREVENTING ADMISSIONS AND READMISSIONS

In people with diabetes, the hospital readmission rate is between 14% and 20%, which is nearly twice that in people without diabetes (148,153). This may result in increased diabetes distress and has significant financial implications. Of people with diabetes who are hospitalized, 30% have two or more hospital stays, and these admissions account for over 50% of hospital costs for diabetes (154). Factors contributing to readmission include male sex, longer duration of prior hospitalization, number of previous hospitalizations, number and severity of comorbidities, and lower socioeconomic and/or educational status; factors that may reduce readmission rates include scheduled home health visits and timely ambulatory follow-up care (148,153). While there is no standard to prevent readmissions, several successful strategies have been reported that identify high-risk individuals and offer some possible solutions (148). These include reaching out to people with ketosis-prone diabetes (155), insulin treatment of individuals with admission A1C $>$9% ($>$75 mmol/mol) (156), and the use of a transitional care model (157). For people with diabetic kidney disease, collaborative person-centered medical homes may decrease risk-adjusted readmission rates (158).

Age is also an important risk factor in hospitalization and readmission among people with diabetes (refer to Section 13, “Older Adults,” for detailed criteria). Successful proactive care transitions from inpatient to outpatient is a key strategy for preventing readmission.

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17. Diabetes Advocacy: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S307–S308 | https://doi.org/10.2337/dc24-S017

*American Diabetes Association Professional Practice Committee**

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Managing the daily health demands of diabetes can be challenging. People living with diabetes should not have to face discrimination due to diabetes. By advocating for the rights of those with diabetes at all levels, the American Diabetes Association (ADA) can help to ensure that they live a healthy and productive life. A strategic goal of the ADA is for more children and adults with diabetes to live free from the burden of discrimination. The ADA is also focused on making sure cost is not a barrier to successful diabetes management.

One tactic for achieving these goals has been to implement the ADA Standards of Care through advocacy-oriented position statements. The ADA publishes evidence-based, peer-reviewed statements on topics such as diabetes and employment, diabetes and driving, insulin access and affordability, and diabetes management in certain settings such as schools, childcare programs, and detention facilities. In addition to the ADA's clinical documents, these advocacy statements are important tools in educating schools, employers, licensing agencies, policy makers, and others about the intersection of diabetes management and the law and for providing scientifically supported policy recommendations.

ADVOCACY STATEMENTS

The following is a partial list of advocacy statements ordered by publication date, with the most recent statement appearing first. A comprehensive list of advocacy statements is available at professional.diabetes.org/content/key-statements-and-reports.

Care of Young Children With Diabetes in the Childcare and Community Setting

Very young children (aged <5 years) with diabetes have legal protections and can be safely cared for by childcare professionals with appropriate training, access to resources, and a communication system with parents/guardians and the child's diabetes health care professional. Refer to the published ADA advocacy statement for information on young children aged <5 years in settings such as childcare centers, preschools, camps, and other programs (1).

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.

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Insulin Access and Affordability

The ADA's Insulin Access and Affordability Working Group compiled public information and convened a series of meetings with stakeholders throughout the insulin supply chain to learn how each entity affects the cost of insulin for the consumer. Their conclusions and recommendations are published in an ADA statement (2).

Diabetes Care in the School Setting

A sizable portion of a child's day is spent in school, so close communication with and training and cooperation of school personnel are essential to optimize diabetes management, safety, and access to all school-sponsored opportunities. Refer to the published ADA position statement for diabetes management information for students with diabetes in elementary and secondary school settings (3).

Diabetes and Driving

People with diabetes who wish to operate motor vehicles are subject to various licensing requirements applied by both state and federal jurisdictions. For an overview of existing licensing rules for people with diabetes, factors that impact driving for this population, and general guidelines for assessing driver fitness and determining appropriate licensing restrictions, refer to the published ADA position statement (4).

Editor's note: Federal commercial driving rules for individuals with insulin-treated diabetes changed on 19 November 2018. These changes will be reflected in a future updated ADA statement.

Diabetes and Employment

Any person with diabetes, whether insulin treated or noninsulin treated, should be eligible for any employment for which they are otherwise qualified. Employment decisions should never be based on generalizations or stereotypes regarding the effects of diabetes. For a general set of guidelines for evaluating individuals with diabetes for employment, including how an assessment should be performed and what changes (accommodations) in the workplace may be needed for an individual with diabetes, refer to the published ADA position statement (5).

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Disclosures: *Standards of Care in Diabetes—2024*

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Committee members disclosed the following financial or other dualities of interest covering the period 12 months before December 2023

Member	Employment	Research grant	Other research support	Speakers bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
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Member	Employment	Research grant	Other research support	Speakers bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
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Member	Employment	Research grant	Other research support	Speakers bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
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*≥$10,000 per year from company to individual. #Grant or contract is to university or other employer. §Nuha A. ElSayed, Raveendhara R. Bannuru, and Robert A. Gabbay are also American Diabetes Association staff.

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